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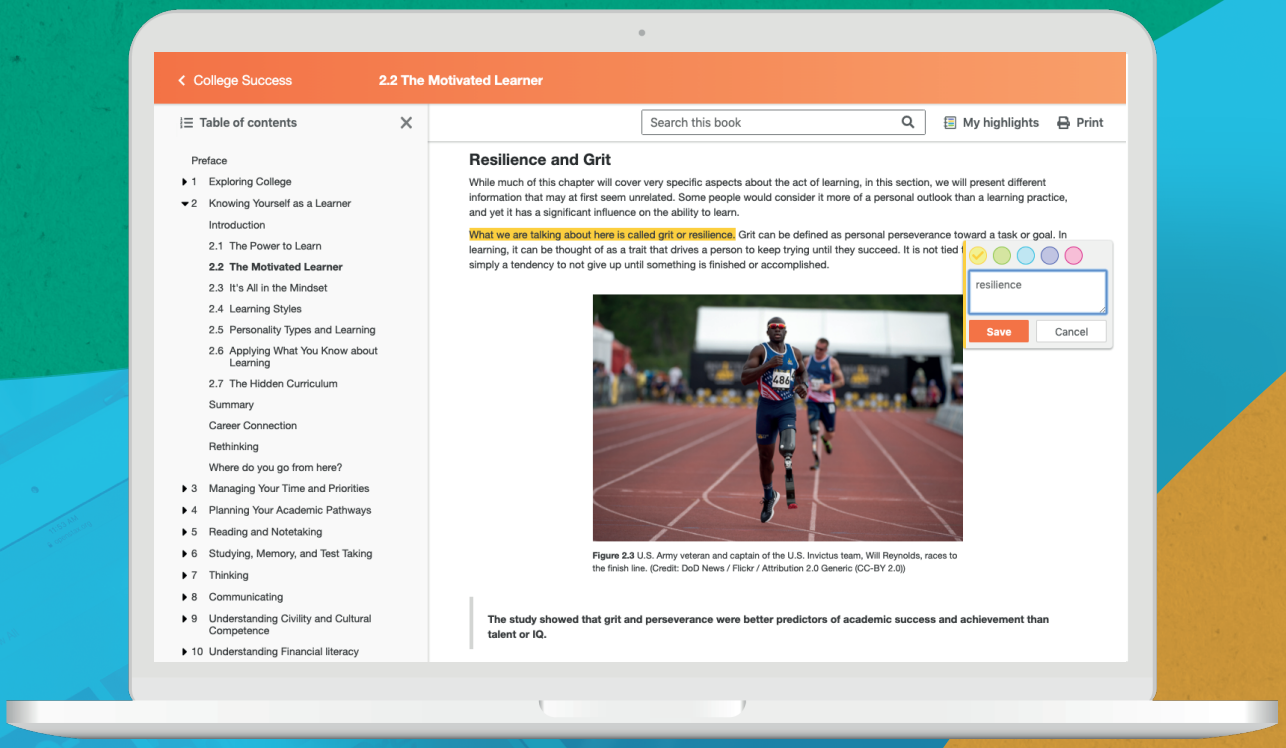
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Unit 5: Energy, Maintenance, and Environmental Exchange
In Chapters 22–26, students discover the interaction between body systems and the outside environment for the exchange of materials, the capture of energy, the release of waste, and the overall maintenance of the internal systems that regulate the exchange. The explanations and illustrations are particularly focused on how structure relates to function.
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Changes to the Second Edition

The **Anatomy and Physiology 2e** revision focuses on inclusive and equitable instruction, scientific accuracy, and enhanced instructor and student support. The improvements have been informed by extensive feedback from adopting faculty, curricular innovators, and equity experts.

The revision includes the following core changes:

- In explanations of endocrine function, reproduction, development, inheritance, and related topics, the second edition is clearer and more accurate in differentiations related to sex, and eliminates incorrect equivalencies and generalizations regarding sex and gender. OpenStax thanks Sam Long and River Suh, founders of Gender-Inclusive Biology, for their extensive guidance and support
- Many of the illustrations have been improved to be more representative of diverse populations. We have also added photos of many conditions, symptoms, and disorders that present differently depending on skin tone. (Note that many of the illustration changes were made prior to the second edition revision.)
- In discussions and illustrations of genetics and inheritance, the text is clearer in its terminology and explanations related to parenting and parental roles.
- Several research references, data, and terminology have been improved to improve representation and currency.

These improvements are designed to create welcoming and inclusive learning experiences and promote scientifically accurate practices that students will encounter in their studies and careers. The additions and changes were made in a manner designed to enrich and support all users while maintaining the general approach of the text. Because OpenStax and our authors are aware of the difficulties posed by reorganization and renumbering, the extensive text and illustration changes have been implemented within the existing structure and organization of the book. A detailed transition guide will be available within the book's Instructor Resources at OpenStax.org.

Pedagogical Foundation and Features

Anatomy and Physiology 2e is designed to promote scientific literacy. Throughout the text, you will find features that engage the students by taking selected topics a step further.

- **Homeostatic Imbalances** discusses the effects and results of imbalances in the body.
- **Disorders** showcases a disorder that is relevant to the body system at hand. This feature may focus on a specific disorder or a set of related disorders.
- **Diseases** showcases a disease that is relevant to the body system at hand.

Additional Resources

Student and Instructor Resources

We've compiled additional resources for both students and instructors, including Getting Started Guides, an instructor solution guide, a curated video guide, and several types of PowerPoint slides and image resources. Instructor resources require a verified instructor account, which you can apply for when you log in or create your account on OpenStax.org. Student resources include guided lecture notes, a student solutions manual, and a pronunciation guide.

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About the Authors

Senior Contributing Authors

J. Gordon Betts, Tyler Junior College
Peter Desaix, University of North Carolina at Chapel Hill
Eddie Johnson, Central Oregon Community College
Jody E. Johnson, Arapahoe Community College
Oksana Korol, Aims Community College
Dean Kruse, Portland Community College
Brandon Poe, Springfield Technical Community College
James A. Wise, Hampton University
Mark Womble, Youngstown State University
Kelly A. Young, California State University, Long Beach

Advisor

Robin J. Heyden

Contributing Authors

Kim Aaronson, Aquarius Institute; Triton College
Lopamudra Agarwal, Augusta Technical College
Gary Allen, Dalhousie University
Robert Allison, McLennan Community College
Heather Armbruster, Southern Union State Community College
Timothy Ballard, University of North Carolina Wilmington
Matthew Barlow, Eastern New Mexico University
William Blaker, Furman University
Julie Bowers, East Tennessee State University
Emily Bradshaw, Florida Southern College
Nishi Bryska, University of North Carolina, Charlotte
Susan Caley Opsal, Illinois Valley Community College
Boyd Campbell, Southwest College of Naturopathic Medicine and Health Sciences
Ann Caplea, Walsh University
Marnie Chapman, University of Alaska, Sitka
Barbara Christie-Pope, Cornell College
Kenneth Crane, Texarkana College
Maurice Culver, Florida State College at Jacksonville
Heather Cushman, Tacoma Community College
Noelle Cutter, Molloy College
Lynnette Danzl-Tauer, Rock Valley College
Jane Davis, Aurora University
AnnMarie DelliPizzi, Dominican College
Susan Dentel, Washtenaw Community College
Pamela Dobbins, Shelton State Community College
Patty Dolan, Pacific Lutheran University
Sondra Dubowsky, McLennan Community College
Peter Dukehart, Three Rivers Community College
Ellen DuPré, Central College
Elizabeth DuPriest, Warner Pacific College
Pam Elf, University of Minnesota
Sharon Ellerton, Queensborough Community College
Carla Endres, Utah State University - College of Eastern Utah: San Juan Campus
Myriam Feldman, Lake Washington Institute of Technology; Cascadia Community College
Greg Fitch, Avila University
Lynn Gargan, Tarant County College
Michael Giangrande, Oakland Community College
Chaya Gopalan, St. Louis College of Pharmacy
Victor Greco, Chattahoochee Technical College
Susanna Heinze, Skagit Valley College
Ann Henninger, Wartburg College
Dale Horeth, Tidewater Community College
Michael Hortsch, University of Michigan
Rosemary Hubbard, Marymount University
Mark Hubley, Prince George's Community College
Branko Jablanovic, College of Lake County
Norman Johnson, University of Massachusetts Amherst
Mark Jonasson, North Arkansas College
Jeff Keyte, College of Saint Mary
William Kleinelp, Middlesex County College

1.1 Overview of Anatomy and Physiology

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare and contrast anatomy and physiology, including their specializations and methods of study
- Discuss the fundamental relationship between anatomy and physiology

Human **anatomy** is the scientific study of the body's structures. Some of these structures are very small and can only be observed and analyzed with the assistance of a microscope. Other larger structures can readily be seen, manipulated, measured, and weighed. The word "anatomy" comes from a Greek root that means "to cut apart." Human anatomy was first studied by observing the exterior of the body and observing the wounds of soldiers and other injuries. Later, physicians were allowed to dissect bodies of the dead to augment their knowledge. When a body is dissected, its structures are cut apart in order to observe their physical attributes and their relationships to one another. Dissection is still used in medical schools, anatomy courses, and in pathology labs. In order to observe structures in living people, however, a number of imaging techniques have been developed. These techniques allow clinicians to visualize structures inside the living body such as a cancerous tumor or a fractured bone.

Like most scientific disciplines, anatomy has areas of specialization. **Gross anatomy** is the study of the larger structures of the body, those visible without the aid of magnification (Figure 1.2 **a**). Macro- means "large," thus, gross anatomy is also referred to as macroscopic anatomy. In contrast, micro- means "small," and **microscopic anatomy** is the study of structures that can be observed only with the use of a microscope or other magnification devices (Figure 1.2 **b**). Microscopic anatomy includes cytology, the study of cells and histology, the study of tissues. As the technology of microscopes has advanced, anatomists have been able to observe smaller and smaller structures of the body, from slices of large structures like the heart, to the three-dimensional structures of large molecules in the body.

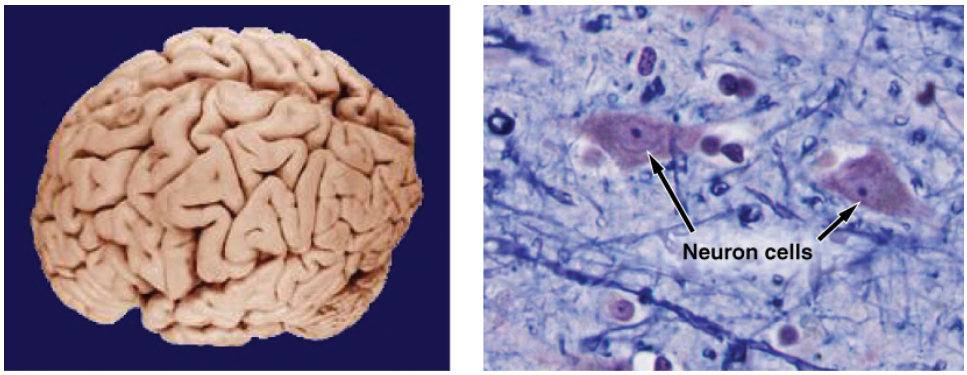


FIGURE 1.2 Gross and Microscopic Anatomy (a) Gross anatomy considers large structures such as the brain. (b) Microscopic anatomy can deal with the same structures, though at a different scale. This is a micrograph of nerve cells from the brain. LM × 1600. (credit a: "WriterHound"/Wikimedia Commons; credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomists take two general approaches to the study of the body's structures: regional and systemic. **Regional anatomy** is the study of the interrelationships of all of the structures in a specific body region, such as the abdomen. Studying regional anatomy helps us appreciate the interrelationships of body structures, such as how muscles, nerves, blood vessels, and other structures work together to serve a particular body region. In contrast, **systemic anatomy** is the study of the structures that make up a discrete body system—that is, a group of structures that work together to perform a unique body function. For example, a systemic anatomical study of the muscular system would consider all of the skeletal muscles of the body.

Whereas anatomy is about structure, physiology is about function. Human **physiology** is the scientific study of the chemistry and physics of the structures of the body and the ways in which they work together to support the functions of life. Much of the study of physiology centers on the body's tendency toward homeostasis. **Homeostasis** is the state of steady internal conditions maintained by living things. The study of physiology certainly includes observation, both with the naked eye and with microscopes, as well as manipulations and measurements. However, current advances in physiology usually depend on carefully designed laboratory experiments that reveal the

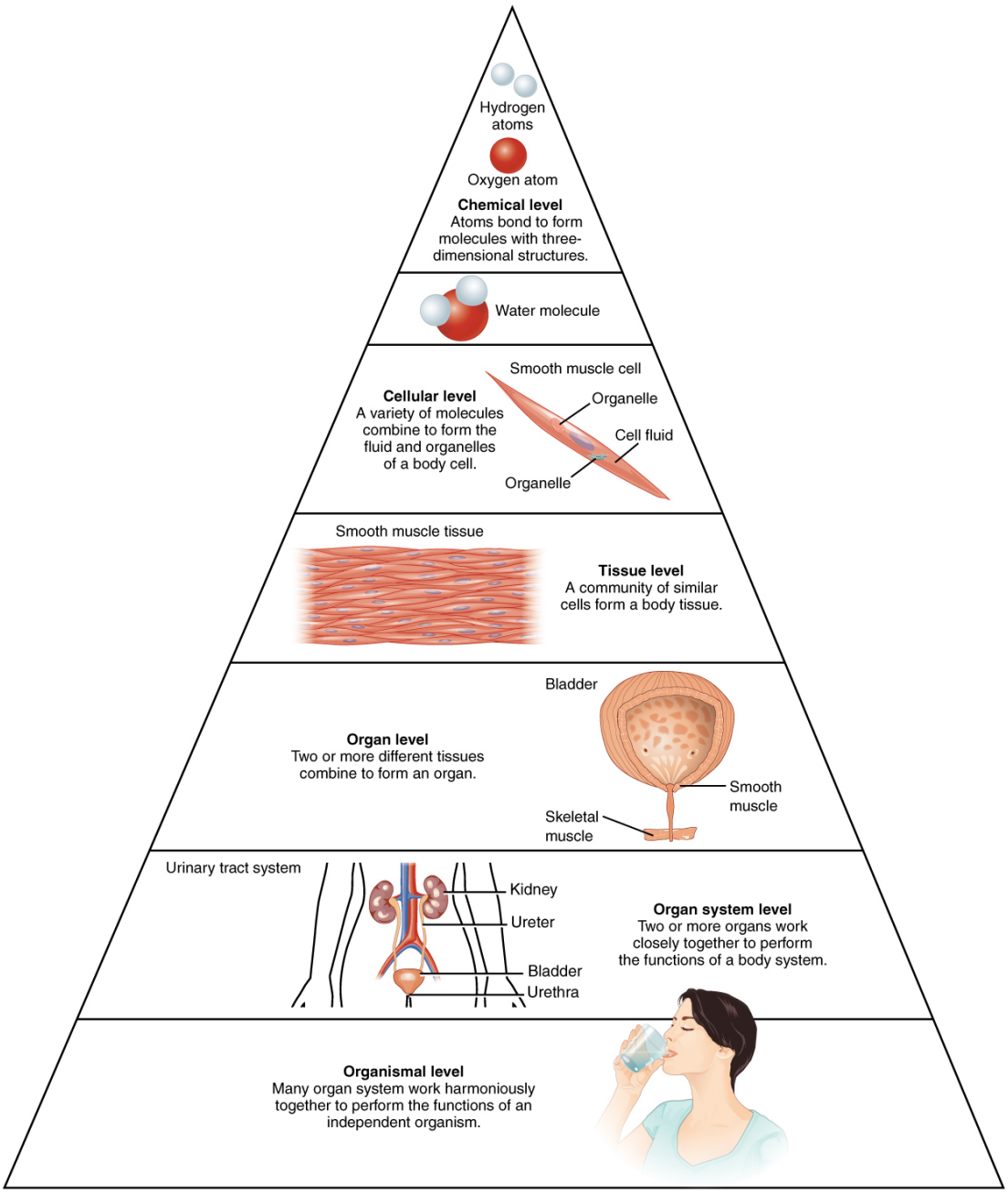


FIGURE 1.3 Levels of Structural Organization of the Human Body The organization of the body often is discussed in terms of six distinct levels of increasing complexity, from the smallest chemical building blocks to a unique human organism.

The Levels of Organization

To study the chemical level of organization, scientists consider the simplest building blocks of matter: subatomic particles, atoms and molecules. All matter in the universe is composed of one or more unique pure substances called elements, familiar examples of which are hydrogen, oxygen, carbon, nitrogen, calcium, and iron. The smallest unit of any of these pure substances (elements) is an atom. Atoms are made up of subatomic particles such as the proton, electron and neutron. Two or more atoms combine to form a molecule, such as the water molecules, proteins, and sugars found in living things. Molecules are the chemical building blocks of all body structures.

A **cell** is the smallest independently functioning unit of a living organism. Even bacteria, which are extremely small, independently-living organisms, have a cellular structure. Each bacterium is a single cell. All living structures of human anatomy contain cells, and almost all functions of human physiology are performed in cells or are initiated by cells.

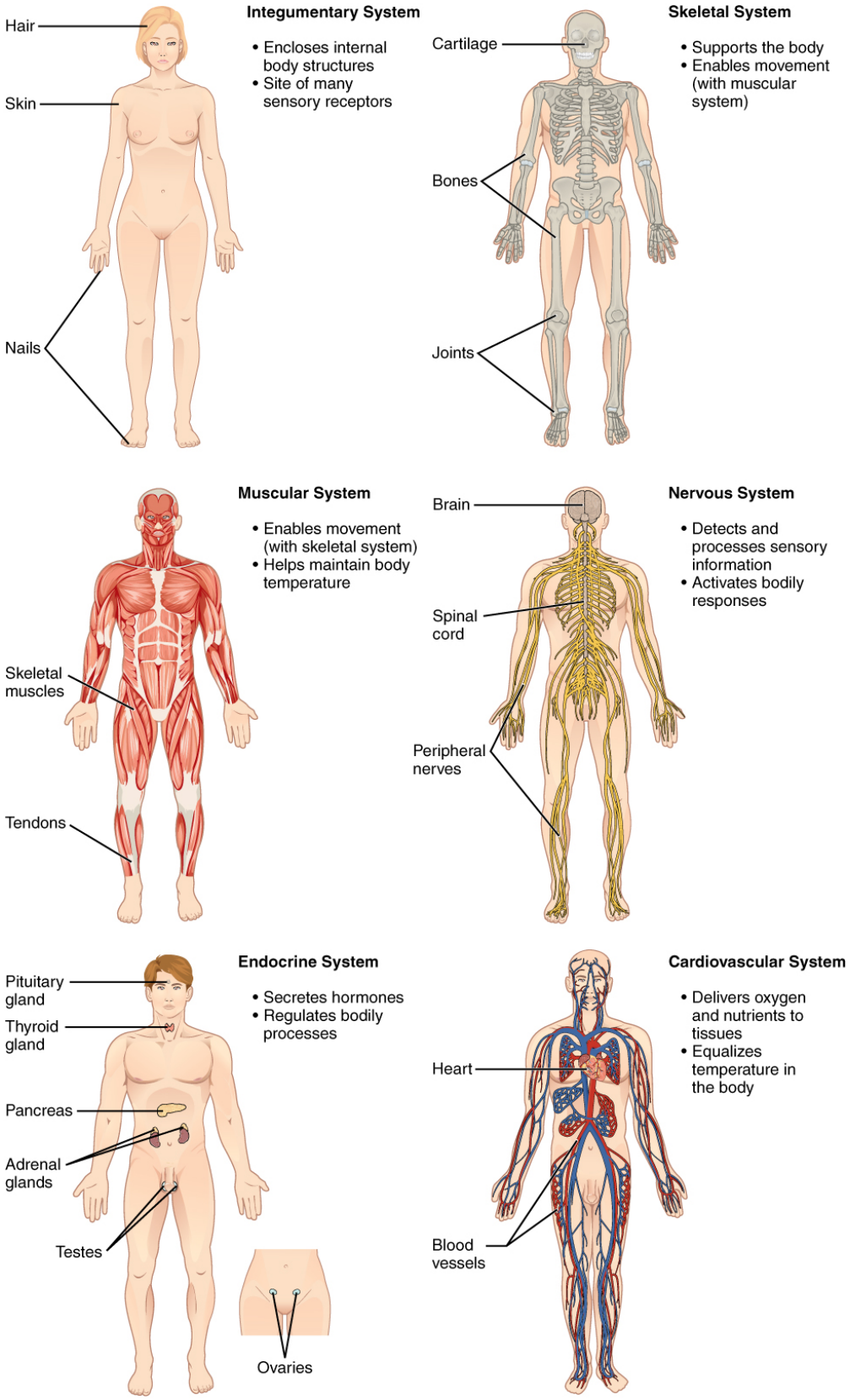


FIGURE 1.4 Organ Systems of the Human Body Organs that work together are grouped into organ systems.

organism.

1.3 Functions of Human Life

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the importance of organization to the function of the human organism
- Distinguish between metabolism, anabolism, and catabolism
- Provide at least two examples of human responsiveness and human movement
- Compare and contrast growth, differentiation, and reproduction

The different organ systems each have different functions and therefore unique roles to perform in physiology. These many functions can be summarized in terms of a few that we might consider definitive of human life: organization, metabolism, responsiveness, movement, development, and reproduction.

Organization

A human body consists of trillions of cells organized in a way that maintains distinct internal compartments. These compartments keep body cells separated from external environmental threats and keep the cells moist and nourished. They also separate internal body fluids from the countless microorganisms that grow on body surfaces, including the lining of certain passageways that connect to the outer surface of the body. The intestinal tract, for example, is home to more bacterial cells than the total of all human cells in the body, yet these bacteria are outside the body and cannot be allowed to circulate freely inside the body.

Cells, for example, have a cell membrane (also referred to as the plasma membrane) that keeps the intracellular environment—the fluids and organelles—separate from the extracellular environment. Blood vessels keep blood inside a closed circulatory system, and nerves and muscles are wrapped in connective tissue sheaths that separate them from surrounding structures. In the chest and abdomen, a variety of internal membranes keep major organs such as the lungs, heart, and kidneys separate from others.

The body's largest organ system is the integumentary system, which includes the skin and its associated structures, such as hair and nails. The surface tissue of skin is a barrier that protects internal structures and fluids from potentially harmful microorganisms and other toxins.

Metabolism

The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: **anabolism** and **catabolism**.

- **Anabolism** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat
- **Catabolism** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.

Taken together, these two processes are called metabolism. **Metabolism** is the sum of all anabolic and catabolic reactions that take place in the body (Figure 1.6). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.



FIGURE 1.7 Marathon Runners Runners demonstrate two characteristics of living humans—responsiveness and movement. Anatomic structures and physiological processes allow runners to coordinate the action of muscle groups and sweat in response to rising internal body temperature. (credit: Phil Roeder/flickr)

Development, growth and reproduction

Development is all of the changes the body goes through in life. Development includes the process of **differentiation**, in which unspecialized cells become specialized in structure and function to perform certain tasks in the body. Development also includes the processes of growth and repair, both of which involve cell differentiation.

Growth is the increase in body size. Humans, like all multicellular organisms, grow by increasing the number of existing cells, increasing the amount of non-cellular material around cells (such as mineral deposits in bone), and, within very narrow limits, increasing the size of existing cells.

Reproduction is the formation of a new organism from parent organisms. In humans, reproduction is carried out by the male and female reproductive systems. Because death will come to all complex organisms, without reproduction, the line of organisms would end.

1.4 Requirements for Human Life

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the role of oxygen and nutrients in maintaining human survival
- Explain why extreme heat and extreme cold threaten human survival
- Explain how the pressure exerted by gases and fluids influences human survival

Humans have been acclimating to life on Earth for at least the past 200,000 years. Earth and its atmosphere have provided us with air to breathe, water to drink, and food to eat, but these are not the only requirements for survival. Although you may rarely think about it, you also cannot live outside of a certain range of temperature and pressure that the surface of our planet and its atmosphere provides. The next sections explore these four requirements of life.

Oxygen

Atmospheric air is only about 20 percent oxygen, but that oxygen is a key component of the chemical reactions that keep the body alive, including the reactions that produce ATP. Brain cells are especially sensitive to lack of oxygen because of their requirement for a high-and-steady production of ATP. Brain damage is likely within five minutes without oxygen, and death is likely within ten minutes.



FIGURE 1.8 Extreme Heat Humans acclimate to some degree to repeated exposure to high temperatures. (credit: McKay Savage/flickr)

The body can also respond effectively to short-term exposure to cold. One response to cold is shivering, which is random muscle movement that generates heat. Another response is increased breakdown of stored energy to generate heat. When that energy reserve is depleted, however, and the core temperature begins to drop significantly, red blood cells will lose their ability to give up oxygen, denying the brain of this critical component of ATP production. This lack of oxygen can cause confusion, lethargy, and eventually loss of consciousness and death. The body responds to cold by reducing blood circulation to the extremities, the hands and feet, in order to prevent blood from cooling there and so that the body's core can stay warm. Even when core body temperature remains stable, however, tissues exposed to severe cold, especially the fingers and toes, can develop frostbite when blood flow to the extremities has been much reduced. This form of tissue damage can be permanent and lead to gangrene, requiring amputation of the affected region.

Everyday Connection

Controlled Hypothermia

As you have learned, the body continuously engages in coordinated physiological processes to maintain a stable temperature. In some cases, however, overriding this system can be useful, or even life-saving. Hypothermia is the clinical term for an abnormally low body temperature (hypo- = "below" or "under"). Controlled hypothermia is clinically induced hypothermia performed in order to reduce the metabolic rate of an organ or of a person's entire body.

Controlled hypothermia often is used, for example, during open-heart surgery because it decreases the metabolic needs of the brain, heart, and other organs, reducing the risk of damage to them. When controlled hypothermia is used clinically, the patient is given medication to prevent shivering. The body is then cooled to 25–32°C (79–89°F). The heart is stopped and an external heart-lung pump maintains circulation to the patient's body. The heart is cooled further and is maintained at a temperature below 15°C (60°F) for the duration of the surgery. This very cold temperature helps the heart muscle to tolerate its lack of blood supply during the surgery.

Some emergency department physicians use controlled hypothermia to reduce damage to the heart in patients who have suffered a cardiac arrest. In the emergency department, the physician induces coma and lowers the patient's body temperature to approximately 91 degrees. This condition, which is maintained for 24 hours, slows the patient's metabolic rate. Because the patient's organs require less blood to function, the heart's workload is reduced.

dissolved in the blood. When pressure is reduced, less gas remains dissolved. You have seen this in effect when you open a carbonated drink. Removing the seal of the bottle reduces the pressure of the gas over the liquid. This in turn causes bubbles as dissolved gases (in this case, carbon dioxide) come out of solution in the liquid.

The most common symptoms of DCS are pain in the joints, with headache and disturbances of vision occurring in 10 percent to 15 percent of cases. Left untreated, very severe DCS can result in death. Immediate treatment is with pure oxygen. The affected person is then moved into a hyperbaric chamber. A hyperbaric chamber is a reinforced, closed chamber that is pressurized to greater than atmospheric pressure. It treats DCS by repressurizing the body so that pressure can then be removed much more gradually. Because the hyperbaric chamber introduces oxygen to the body at high pressure, it increases the concentration of oxygen in the blood. This has the effect of replacing some of the nitrogen in the blood with oxygen, which is easier to tolerate out of solution.

The dynamic pressure of body fluids is also important to human survival. For example, blood pressure, which is the pressure exerted by blood as it flows within blood vessels, must be great enough to enable blood to reach all body tissues, and yet low enough to ensure that the delicate blood vessels can withstand the friction and force of the pulsating flow of pressurized blood.

1.5 Homeostasis

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the role of homeostasis in healthy functioning
- Contrast negative and positive feedback, giving one physiologic example of each mechanism

Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A **set point** is the physiological value around which the normal range fluctuates. A **normal range** is the restricted set of values that is optimally healthful and stable. For example, the set point for normal human body temperature is approximately 37°C (98.6°F) Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a normal range a few degrees above and below that point. Control centers in the brain and other parts of the body monitor and react to deviations from homeostasis using negative feedback. **Negative feedback** is a mechanism that reverses a deviation from the set point. Therefore, negative feedback maintains body parameters within their normal range. The maintenance of homeostasis by negative feedback goes on throughout the body at all times, and an understanding of negative feedback is thus fundamental to an understanding of human physiology.

Negative Feedback

A negative feedback system has three basic components (Figure 1.10**a**). A **sensor**, also referred to a receptor, is a component of a feedback system that monitors a physiological value. This value is reported to the control center. The **control center** is the component in a feedback system that compares the value to the normal range. If the value deviates too much from the set point, then the control center activates an effector. An **effector** is the component in a feedback system that causes a change to reverse the situation and return the value to the normal range.

INTERACTIVE LINK

Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this video (http://openstax.org/l/H2Ocon) to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

Positive Feedback

Positive feedback intensifies a change in the body's physiological condition rather than reversing it. A deviation from the normal range results in more change, and the system moves farther away from the normal range. Positive feedback in the body is normal only when there is a definite end point. Childbirth and the body's response to blood loss are two examples of positive feedback loops that are normal but are activated only when needed.

Childbirth at full term is an example of a situation in which the maintenance of the existing body state is not desired. Enormous changes in a person's body are required to expel the baby at the end of pregnancy. And the events of childbirth, once begun, must progress rapidly to a conclusion or the life of a person giving bith and the baby are at risk. The extreme muscular work of labor and delivery are the result of a positive feedback system (Figure 1.11).

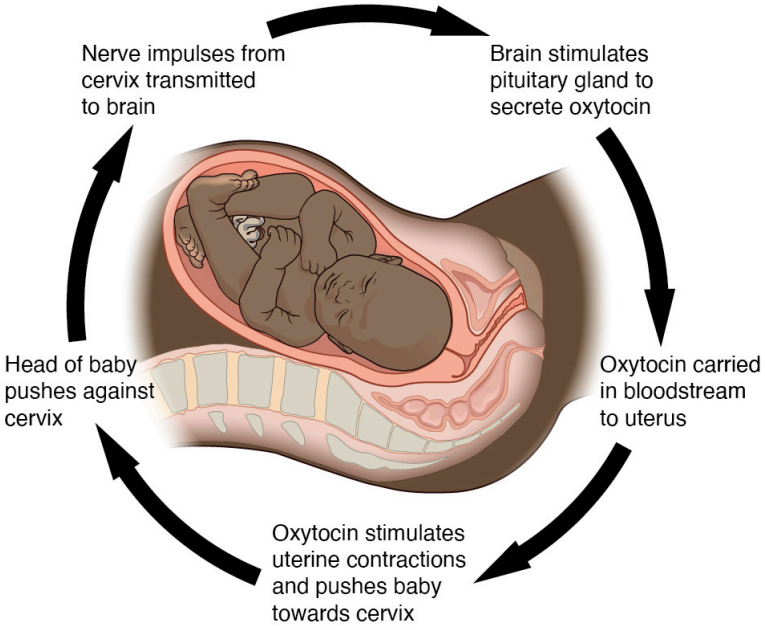


FIGURE 1.11 Positive Feedback Loop Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

The first contractions of labor (the stimulus) push the baby toward the cervix (the lowest part of the uterus). The cervix contains stretch-sensitive nerve cells that monitor the degree of stretching (the sensors). These nerve cells send messages to the brain, which in turn causes the pituitary gland at the base of the brain to release the hormone oxytocin into the bloodstream. Oxytocin causes stronger contractions of the smooth muscles in of the uterus (the effectors), pushing the baby further down the birth canal. This causes even greater stretching of the cervix. The cycle of stretching, oxytocin release, and increasingly more forceful contractions stops only when the baby is born. At this point, the stretching of the cervix halts, stopping the release of oxytocin.

A second example of positive feedback centers on reversing extreme damage to the body. Following a penetrating wound, the most immediate threat is excessive blood loss. Less blood circulating means reduced blood pressure and reduced perfusion (penetration of blood) to the brain and other vital organs. If perfusion is severely reduced, vital organs will shut down and the person will die. The body responds to this potential catastrophe by releasing substances in the injured blood vessel wall that begin the process of blood clotting. As each step of clotting occurs,

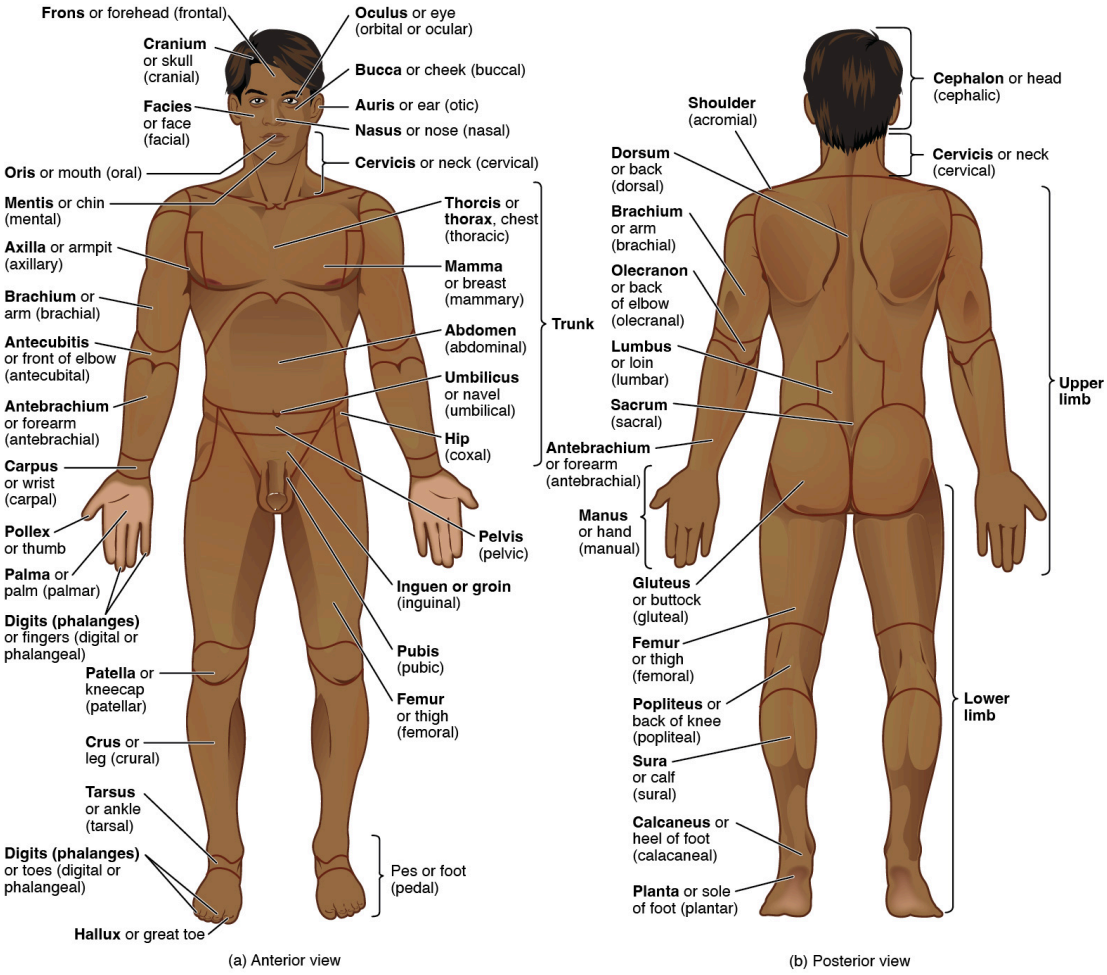


FIGURE 1.12 Regions of the Human Body The human body is shown in anatomical position in an (a) anterior view and a (b) posterior view. The regions of the body are labeled in boldface.

A body that is lying down is described as either prone or supine. **Prone** describes a face-down orientation, and **supine** describes a face up orientation. These terms are sometimes used in describing the position of the body during specific physical examinations or surgical procedures.

Regional Terms

The human body's numerous regions have specific terms to help increase precision (see Figure 1.12). Notice that the term "brachium" or "arm" is reserved for the "upper arm" and "antebrachium" or "forearm" is used rather than "lower arm." Similarly, "femur" or "thigh" is correct, and "leg" or "crus" is reserved for the portion of the lower limb between the knee and the ankle. You will be able to describe the body's regions using the terms from the figure.

Directional Terms

Certain directional anatomical terms appear throughout this and any other anatomy textbook (Figure 1.13). These terms are essential for describing the relative locations of different body structures. For instance, an anatomist might describe one band of tissue as "inferior to" another or a physician might describe a tumor as "superficial to" a deeper body structure. Commit these terms to memory to avoid confusion when you are studying or describing the locations of particular body parts.

- **Anterior** (or **ventral**) Describes the front or direction toward the front of the body. The toes are anterior to the foot.
- **Posterior** (or **dorsal**) Describes the back or direction toward the back of the body. The popliteus is posterior to the patella.
- **Superior** (or **cranial**) describes a position above or higher than another part of the body proper. The orbits are superior to the oris.

Transverse planes produce images referred to as cross sections.

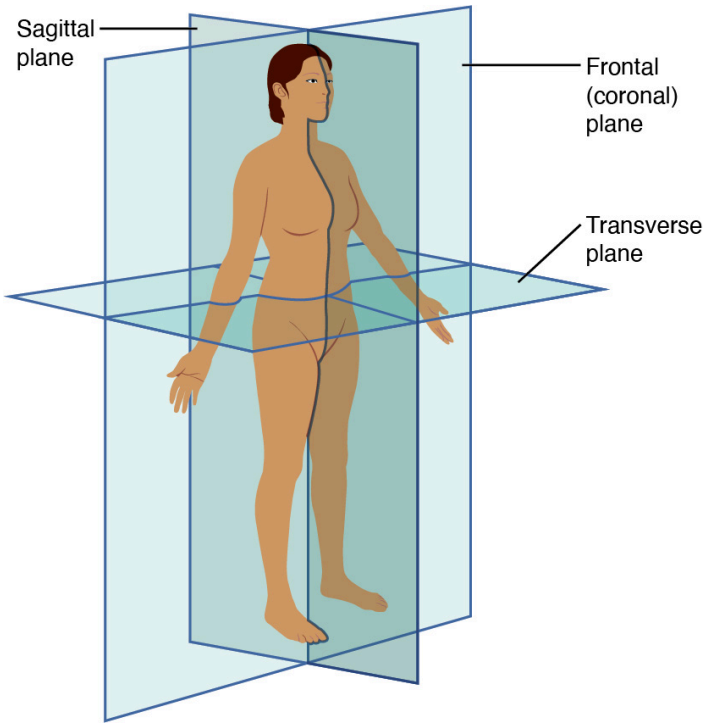


FIGURE 1.14 Planes of the Body The three planes most commonly used in anatomical and medical imaging are the sagittal, frontal (or coronal), and transverse plane.

Body Cavities and Serous Membranes

The body maintains its internal organization by means of membranes, sheaths, and other structures that separate compartments. The **dorsal (posterior) cavity** and the **ventral (anterior) cavity** are the largest body compartments (Figure 1.15). These cavities contain and protect delicate internal organs, and the ventral cavity allows for significant changes in the size and shape of the organs as they perform their functions. The lungs, heart, stomach, and intestines, for example, can expand and contract without distorting other tissues or disrupting the activity of nearby organs.

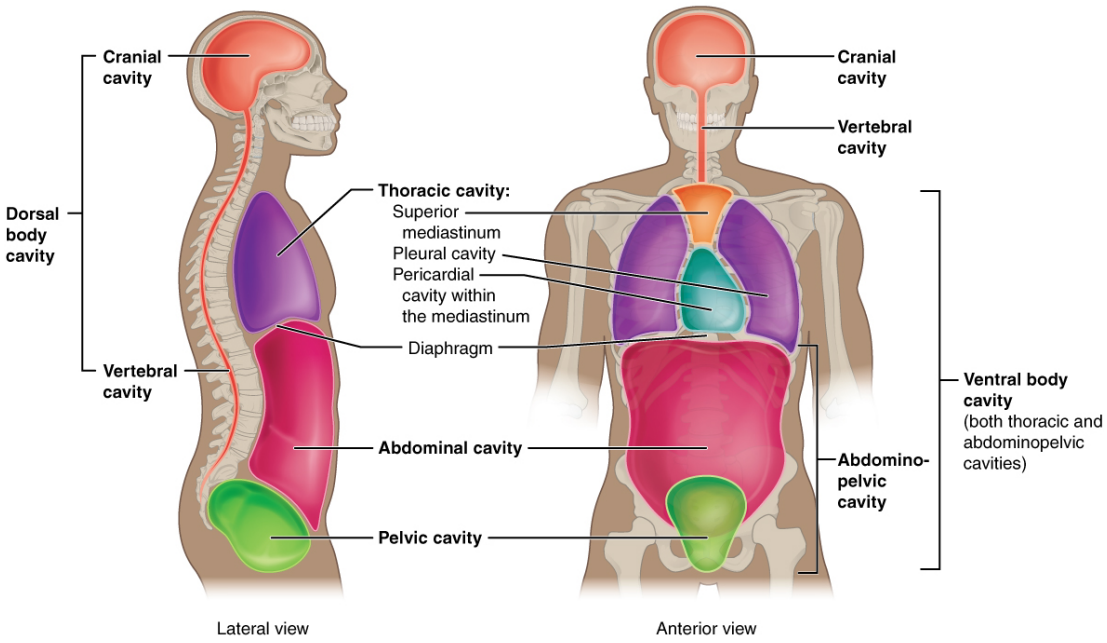


FIGURE 1.15 Dorsal and Ventral Body Cavities The ventral cavity includes the thoracic and abdominopelvic cavities and their subdivisions. The dorsal cavity includes the cranial and spinal cavities.

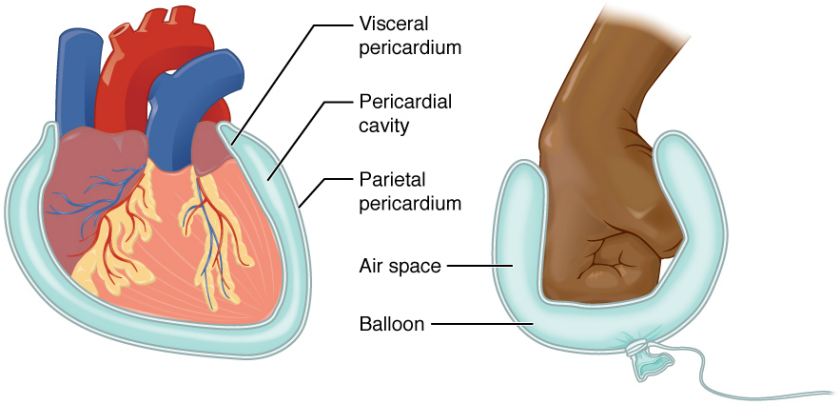


FIGURE 1.17 Serous Membrane Serous membrane lines the pericardial cavity and reflects back to cover the heart—much the same way that an underinflated balloon would form two layers surrounding a fist.

There are three serous cavities and their associated membranes. The **pleura** is the serous membrane that encloses the pleural cavity; the pleural cavity surrounds the lungs. The **pericardium** is the serous membrane that encloses the pericardial cavity; the pericardial cavity surrounds the heart. The **peritoneum** is the serous membrane that encloses the peritoneal cavity; the peritoneal cavity surrounds several organs in the abdominopelvic cavity. The serous membranes form fluid-filled sacs, or cavities, that are meant to cushion and reduce friction on internal organs when they move, such as when the lungs inflate or the heart beats. Both the parietal and visceral serosa secrete the thin, slippery serous fluid located within the serous cavities. The pleural cavity reduces friction between the lungs and the body wall. Likewise, the pericardial cavity reduces friction between the heart and the wall of the pericardium. The peritoneal cavity reduces friction between the abdominal and pelvic organs and the body wall. Therefore, serous membranes provide additional protection to the viscera they enclose by reducing friction that could lead to inflammation of the organs.

1.7 Medical Imaging

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the uses and drawbacks of X-ray imaging
- Identify four modern medical imaging techniques and how they are used

For thousands of years, fear of the dead and legal sanctions limited the ability of anatomists and physicians to study the internal structures of the human body. An inability to control bleeding, infection, and pain made surgeries infrequent, and those that were performed—such as wound suturing, amputations, tooth and tumor removals, skull drilling, and cesarean births—did not greatly advance knowledge about internal anatomy. Theories about the function of the body and about disease were therefore largely based on external observations and imagination. During the fourteenth and fifteenth centuries, however, the detailed anatomical drawings of Italian artist and anatomist Leonardo da Vinci and Flemish anatomist Andreas Vesalius were published, and interest in human anatomy began to increase. Medical schools began to teach anatomy using human dissection; although some resorted to grave robbing to obtain corpses. Laws were eventually passed that enabled students to dissect the corpses of criminals and those who donated their bodies for research. Still, it was not until the late nineteenth century that medical researchers discovered non-surgical methods to look inside the living body.

X-Rays

German physicist Wilhelm Röntgen (1845–1923) was experimenting with electrical current when he discovered that a mysterious and invisible “ray” would pass through his flesh but leave an outline of his bones on a screen coated with a metal compound. In 1895, Röntgen made the first durable record of the internal parts of a living human: an “X-ray” image (as it came to be called) of his wife’s hand. Scientists around the world quickly began their own experiments with X-rays, and by 1900, X-rays were widely used to detect a variety of injuries and diseases. In 1901, Röntgen was awarded the first Nobel Prize for physics for his work in this field.

The **X-ray** is a form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids

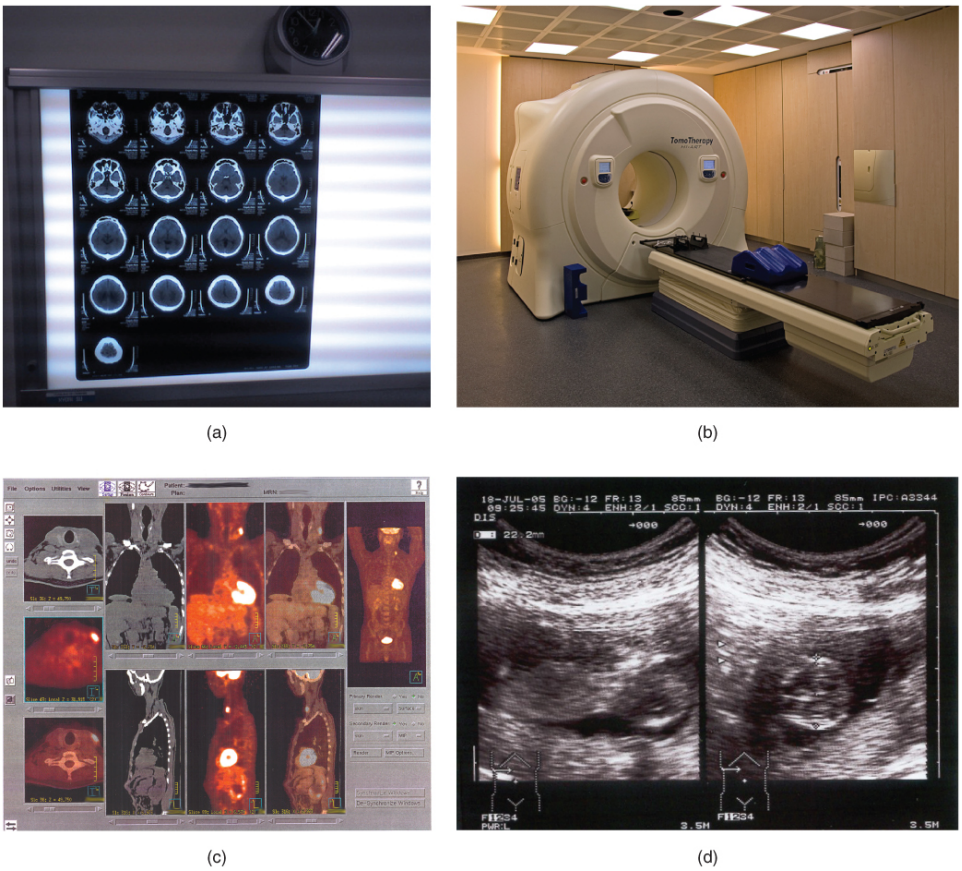


FIGURE 1.19 Medical Imaging Techniques (a) The results of a CT scan of the head are shown as successive transverse sections. (b) An MRI machine generates a magnetic field around a patient. (c) PET scans use radiopharmaceuticals to create images of active blood flow and physiologic activity of the organ or organs being targeted. (d) Ultrasound technology is used to monitor pregnancies because it is the least invasive of imaging techniques and uses no electromagnetic radiation. (credit a: Akira Ohgaki/flickr; credit b: "Digital Cate"/flickr; credit c: "Raziel"/Wikimedia Commons; credit d: "Isis"/Wikimedia Commons)

Since 1970, the development of more powerful computers and more sophisticated software has made CT scanning routine for many types of diagnostic evaluations. It is especially useful for soft tissue scanning, such as of the brain and the thoracic and abdominal viscera. Its level of detail is so precise that it can allow physicians to measure the size of a mass down to a millimeter. The main disadvantage of CT scanning is that it exposes patients to a dose of radiation many times higher than that of X-rays. In fact, children who undergo CT scans are at increased risk of developing cancer, as are adults who have multiple CT scans.

INTERACTIVE LINK

A CT or CAT scan relies on a circling scanner that revolves around the patient's body. Watch this video (http://openstax.org/l/CATscan) to learn more about CT and CAT scans. What type of radiation does a CT scanner use?

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique based on a phenomenon of nuclear physics discovered in the 1930s, in which matter exposed to magnetic fields and radio waves was found to emit radio signals. In 1970, a physician and researcher named Raymond Damadian noticed that malignant (cancerous) tissue gave off different signals than normal body tissue. He applied for a patent for the first MRI scanning device, which was in use clinically by the early 1980s. The early MRI scanners were crude, but advances in digital computing and electronics led to their advancement over any other technique for precise imaging, especially to discover tumors. MRI also has the major advantage of not exposing patients to radiation.

Drawbacks of MRI scans include their much higher cost, and patient discomfort with the procedure. The MRI scanner subjects the patient to such powerful electromagnets that the scan room must be shielded. The patient

Key Terms

abdominopelvic cavity division of the anterior (ventral) cavity that houses the abdominal and pelvic viscera
anabolism assembly of more complex molecules from simpler molecules
anatomical position standard reference position used for describing locations and directions on the human body
anatomy science that studies the form and composition of the body's structures
anterior describes the front or direction toward the front of the body; also referred to as ventral
anterior cavity larger body cavity located anterior to the posterior (dorsal) body cavity; includes the serous membrane-lined pleural cavities for the lungs, pericardial cavity for the heart, and peritoneal cavity for the abdominal and pelvic organs; also referred to as ventral cavity
catabolism breaking down of more complex molecules into simpler molecules
caudal describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column); also referred to as inferior
cell smallest independently functioning unit of all organisms; in animals, a cell contains cytoplasm, composed of fluid and organelles
computed tomography (CT) medical imaging technique in which a computer-enhanced cross-sectional X-ray image is obtained
control center compares values to their normal range; deviations cause the activation of an effector
cranial describes a position above or higher than another part of the body proper; also referred to as superior
cranial cavity division of the posterior (dorsal) cavity that houses the brain
deep describes a position farther from the surface of the body
development changes an organism goes through during its life
differentiation process by which unspecialized cells become specialized in structure and function
distal describes a position farther from the point of attachment or the trunk of the body
dorsal describes the back or direction toward the back of the body; also referred to as posterior
dorsal cavity posterior body cavity that houses the brain and spinal cord; also referred to the posterior body cavity
effector organ that can cause a change in a value
frontal plane two-dimensional, vertical plane that divides the body or organ into anterior and posterior portions
gross anatomy study of the larger structures of the body, typically with the unaided eye; also referred to macroscopic anatomy
growth process of increasing in size
homeostasis steady state of body systems that living organisms maintain
inferior describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column); also referred to as caudal
lateral describes the side or direction toward the side of the body
magnetic resonance imaging (MRI) medical imaging technique in which a device generates a magnetic field to obtain detailed sectional images of the internal structures of the body
medial describes the middle or direction toward the middle of the body
metabolism sum of all of the body's chemical reactions
microscopic anatomy study of very small structures of the body using magnification
negative feedback homeostatic mechanism that tends to stabilize an upset in the body's physiological condition by preventing an excessive response to a stimulus, typically as the stimulus is removed
normal range range of values around the set point that do not cause a reaction by the control center
nutrient chemical obtained from foods and beverages that is critical to human survival
organ functionally distinct structure composed of two or more types of tissues
organ system group of organs that work together to carry out a particular function
organism living being that has a cellular structure and that can independently perform all physiologic functions necessary for life
pericardium sac that encloses the heart
peritoneum serous membrane that lines the abdominopelvic cavity and covers the organs found there
physiology science that studies the chemistry, biochemistry, and physics of the body's functions
plane imaginary two-dimensional surface that passes through the body
pleura serous membrane that lines the pleural cavity and covers the lungs
positive feedback mechanism that intensifies a change in the body's physiological condition in

consciously controlled. They occur continuously to build, maintain, and sustain life. These processes include: organization, in terms of the maintenance of essential body boundaries; metabolism, including energy transfer via anabolic and catabolic reactions; responsiveness; movement; and growth, differentiation, reproduction, and renewal.

1.4 Requirements for Human Life

Humans cannot survive for more than a few minutes without oxygen, for more than several days without water, and for more than several weeks without carbohydrates, lipids, proteins, vitamins, and minerals. Although the body can respond to high temperatures by sweating and to low temperatures by shivering and increased fuel consumption, long-term exposure to extreme heat and cold is not compatible with survival. The body requires a precise atmospheric pressure to maintain its gases in solution and to facilitate respiration—the intake of oxygen and the release of carbon dioxide. Humans also require blood pressure high enough to ensure that blood reaches all body tissues but low enough to avoid damage to blood vessels.

1.5 Homeostasis

Homeostasis is the activity of cells throughout the body to maintain the physiological state within a narrow range that is compatible with life. Homeostasis is regulated by negative feedback loops and, much less frequently, by positive feedback loops. Both have the same components of a stimulus, sensor, control center, and effector; however, negative feedback loops work to prevent an excessive response to the stimulus, whereas positive feedback loops intensify the response until an end point is reached.

1.6 Anatomical Terminology

Ancient Greek and Latin words are used to build anatomical terms. A standard reference position for mapping the body's structures is the normal anatomical position. Regions of the body are identified using terms such as "occipital" that are more precise than common words and phrases such as "the back of the head." Directional terms such as anterior and posterior are essential for accurately describing the relative locations of body structures. Images of the body's interior commonly align along one of three planes: the sagittal, frontal, or transverse. The body's organs are organized in one of two main cavities—dorsal (also referred to posterior) and ventral (also referred to anterior)—which are further sub-divided according to the structures present in each area. The serous membranes have two layers—parietal and visceral—surrounding a fluid filled space. Serous membranes cover the lungs (pleural serosa), heart (pericardial serosa), and some abdominopelvic organs (peritoneal serosa).

1.7 Medical Imaging

Detailed anatomical drawings of the human body first became available in the fifteenth and sixteenth centuries; however, it was not until the end of the nineteenth century, and the discovery of X-rays, that anatomists and physicians discovered non-surgical methods to look inside a living body. Since then, many other techniques, including CT scans, MRI scans, PET scans, and ultrasonography, have been developed, providing more accurate and detailed views of the form and function of the human body.

Interactive Link Questions

1. View this animation (http://openstax.org/l/metabolic) to learn more about metabolic processes. What kind of catabolism occurs in the heart?
2. Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this video (http://openstax.org/l/H2Ocon) to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?
3. A CT or CAT scan relies on a circling scanner that revolves around the patient's body. Watch this video (http://openstax.org/l/CATscan) to learn more about CT and CAT scans. What type of radiation does a CT scanner use?
4. A patient undergoing an MRI is surrounded by a tube-shaped scanner. Watch this video (http://openstax.org/l/MRI) to learn more about MRIs. What is the function of magnets in an MRI?
5. PET relies on radioactive substances administered several minutes before the scan. Watch this video (http://openstax.org/l/PET) to learn more about PET. How is PET used in chemotherapy?

19. Which of the following is an example of a normal physiologic process that uses a positive feedback loop?
   a. blood pressure regulation
   b. childbirth
   c. regulation of fluid balance
   d. temperature regulation

20. What is the position of the body when it is in the "normal anatomical position?"
   a. The person is prone with upper limbs, including palms, touching sides and lower limbs touching at sides.
   b. The person is standing facing the observer, with upper limbs extended out at a ninety-degree angle from the torso and lower limbs in a wide stance with feet pointing laterally
   c. The person is supine with upper limbs, including palms, touching sides and lower limbs touching at sides.
   d. None of the above

21. To make a banana split, you halve a banana into two long, thin, right and left sides along the _____.
   a. coronal plane
   b. longitudinal plane
   c. midsagittal plane
   d. transverse plane

22. The lumbar region is _____.
   a. inferior to the gluteal region
   b. inferior to the umbilical region
   c. superior to the cervical region
   d. superior to the popliteal region

23. The heart is within the _____.
   a. cranial cavity
   b. mediastinum
   c. posterior (dorsal) cavity
   d. All of the above

24. In 1901, Wilhelm Röntgen was the first person to win the Nobel Prize for physics. For what discovery did he win?
   a. nuclear physics
   b. radiopharmaceuticals
   c. the link between radiation and cancer
   d. X-rays

25. Which of the following imaging techniques would be best to use to study the uptake of nutrients by rapidly multiplying cancer cells?
   a. CT
   b. MRI
   c. PET
   d. ultrasonography

26. Which of the following imaging studies can be used most safely during pregnancy?
   a. CT scans
   b. PET scans
   c. ultrasounds
   d. X-rays

27. What are two major disadvantages of MRI scans?
   a. release of radiation and poor quality images
   b. high cost and the need for shielding from the magnetic signals
   c. can only view metabolically active tissues and inadequate availability of equipment
   d. release of radiation and the need for a patient to be confined to metal tube for up to 30 minutes

Critical Thinking Questions

28. Name at least three reasons to study anatomy and physiology.

29. For whom would an appreciation of the structural characteristics of the human heart come more easily: an alien who lands on Earth, abducts a human, and dissects his heart, or an anatomy and physiology student performing a dissection of the heart on her very first day of class? Why?

30. Name the six levels of organization of the human body.

31. The and the testes are a part of which body system? Can these organs be members of more than one organ system? Why or why not?

32. Explain why the smell of smoke when you are sitting at a campfire does not trigger alarm, but the smell of smoke in your residence hall does.

33. Identify three different ways that growth can occur in the human body.

34. When you open a bottle of sparkling water, the carbon dioxide gas in the bottle form bubbles. If the bottle is left open, the water will eventually "go flat." Explain these phenomena in terms of atmospheric pressure.

35. On his midsummer trek through the desert, Josh ran out of water. Why is this particularly dangerous?

atoms, the basic units of matter, determine the characteristics of elements by the number of protons, neutrons, and electrons in the atoms. The chapter then builds the framework of life from there.

2.1 Elements and Atoms: The Building Blocks of Matter

LEARNING OBJECTIVES

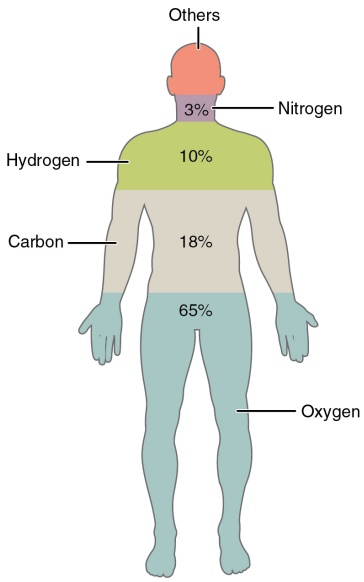
By the end of this section, you will be able to:

- Discuss the relationships between matter, mass, elements, compounds, atoms, and subatomic particles
- Distinguish between atomic number and mass number
- Identify the key distinction between isotopes of the same element
- Explain how electrons occupy electron shells and their contribution to an atom's relative stability

The substance of the universe—from a grain of sand to a star—is called **matter**. Scientists define matter as anything that occupies space and has mass. An object's mass and its weight are related concepts, but not quite the same. An object's mass is the amount of matter contained in the object, and the object's mass is the same whether that object is on Earth or in the zero-gravity environment of outer space. An object's weight, on the other hand, is its mass as affected by the pull of gravity. Where gravity strongly pulls on an object's mass its weight is greater than it is where gravity is less strong. An object of a certain mass weighs less on the moon, for example, than it does on Earth because the gravity of the moon is less than that of Earth. In other words, weight is variable, and is influenced by gravity. A piece of cheese that weighs a pound on Earth weighs only a few ounces on the moon.

Elements and Compounds

All matter in the natural world is composed of one or more of the 92 fundamental substances called elements. An **element** is a pure substance that is distinguished from all other matter by the fact that it cannot be created or broken down by ordinary chemical means. While your body can assemble many of the chemical compounds needed for life from their constituent elements, it cannot make elements. They must come from the environment. A familiar example of an element that you must take in is calcium (Ca). Calcium is essential to the human body; it is absorbed and used for a number of processes, including strengthening bones. When you consume dairy products your digestive system breaks down the food into components small enough to cross into the bloodstream. Among these is calcium, which, because it is an element, cannot be broken down further. The elemental calcium in cheese, therefore, is the same as the calcium that forms your bones. Some other elements you might be familiar with are oxygen, sodium, and iron. The elements in the human body are shown in Figure 2.2, beginning with the most abundant: oxygen (O), carbon (C), hydrogen (H), and nitrogen (N). Each element's name can be replaced by a one- or two-letter symbol; you will become familiar with some of these during this course. All the elements in your body are derived from the foods you eat and the air you breathe.



Element	Symbol	Percentage in Body
Oxygen	O	65.0
Carbon	C	18.5
Hydrogen	H	9.5
Nitrogen	N	3.2
Calcium	Ca	1.5
Phosphorus	P	1.0
Potassium	K	0.4
Sulfur	S	0.3
Sodium	Na	0.2
Chlorine	Cl	0.2
Magnesium	Mg	0.1
Trace elements include boron (B), chromium (Cr), cobalt (Co), copper (Cu), fluorine (F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), silicon (Si), tin (Sn), vanadium (V), and zinc (Zn).		less than 1.0

FIGURE 2.2 Elements of the Human Body The main elements that compose the human body are shown from most abundant to least abundant.

neutral. Just as a magnet sticks to a steel refrigerator because their opposite charges attract, the positively charged protons attract the negatively charged electrons. This mutual attraction gives the atom some structural stability. The attraction by the positively charged nucleus helps keep electrons from straying far. The number of protons and electrons within a neutral atom are equal, thus, the atom's overall charge is balanced.

Atomic Number and Mass Number

An atom of carbon is unique to carbon, but a proton of carbon is not. One proton is the same as another, whether it is found in an atom of carbon, sodium (Na), or iron (Fe). The same is true for neutrons and electrons. So, what gives an element its distinctive properties—what makes carbon so different from sodium or iron? The answer is the unique quantity of protons each contains. Carbon by definition is an element whose atoms contain six protons. No other element has exactly six protons in its atoms. Moreover, *all* atoms of carbon, whether found in your liver or in a lump of coal, contain six protons. Thus, the **atomic number**, which is the number of protons in the nucleus of the atom, identifies the element. Because an atom usually has the same number of electrons as protons, the atomic number identifies the usual number of electrons as well.

In their most common form, many elements also contain the same number of neutrons as protons. The most common form of carbon, for example, has six neutrons as well as six protons, for a total of 12 subatomic particles in its nucleus. An element's **mass number** is the sum of the number of protons and neutrons in its nucleus. So the most common form of carbon's mass number is 12. (Electrons have so little mass that they do not appreciably contribute to the mass of an atom.) Carbon is a relatively light element. Uranium (U), in contrast, has a mass number of 238 and is referred to as a heavy metal. Its atomic number is 92 (it has 92 protons) but it contains 146 neutrons; it has the most mass of all the naturally occurring elements.

The **periodic table of the elements**, shown in Figure 2.4, is a chart identifying the 92 elements found in nature, as well as several larger, unstable elements discovered experimentally. The elements are arranged in order of their atomic number, with hydrogen and helium at the top of the table, and the more massive elements below. The periodic table is a useful device because for each element, it identifies the chemical symbol, the atomic number, and the mass number, while organizing elements according to their propensity to react with other elements. The number of protons and electrons in an element are equal. The number of protons and neutrons may be equal for some elements, but are not equal for all.

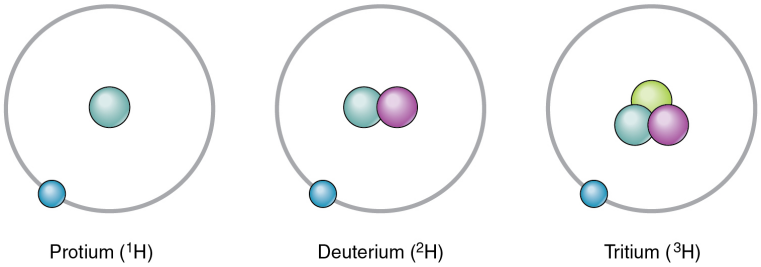


FIGURE 2.5 Isotopes of Hydrogen Protium, designated ^{1}H, has one proton and no neutrons. It is by far the most abundant isotope of hydrogen in nature. Deuterium, designated ^{2}H, has one proton and one neutron. Tritium, designated ^{3}H, has two neutrons.

An isotope that contains more than the usual number of neutrons is referred to as a heavy isotope. An example is ^{14}C. Heavy isotopes tend to be unstable, and unstable isotopes are radioactive. A **radioactive isotope** is an isotope whose nucleus readily decays, giving off subatomic particles and electromagnetic energy. Different radioactive isotopes (also called radioisotopes) differ in their half-life, the time it takes for half of any size sample of an isotope to decay. For example, the half-life of tritium—a radioisotope of hydrogen—is about 12 years, indicating it takes 12 years for half of the tritium nuclei in a sample to decay. Excessive exposure to radioactive isotopes can damage human cells and even cause cancer and birth defects, but when exposure is controlled, some radioactive isotopes can be useful in medicine. For more information, see the Career Connections.

CAREER CONNECTION

Interventional Radiologist

The controlled use of radioisotopes has advanced medical diagnosis and treatment of disease. Interventional radiologists are physicians who treat disease by using minimally invasive techniques involving radiation. Many conditions that could once only be treated with a lengthy and traumatic operation can now be treated non-surgically, reducing the cost, pain, length of hospital stay, and recovery time for patients. For example, in the past, the only options for a patient with one or more tumors in the liver were surgery and chemotherapy (the administration of drugs to treat cancer). Some liver tumors, however, are difficult to access surgically, and others could require the surgeon to remove too much of the liver. Moreover, chemotherapy is highly toxic to the liver, and certain tumors do not respond well to it anyway. In some such cases, an interventional radiologist can treat the tumors by disrupting their blood supply, which they need if they are to continue to grow. In this procedure, called radioembolization, the radiologist accesses the liver with a fine needle, threaded through one of the patient's blood vessels. The radiologist then inserts tiny radioactive "seeds" into the blood vessels that supply the tumors. In the days and weeks following the procedure, the radiation emitted from the seeds destroys the vessels and directly kills the tumor cells in the vicinity of the treatment.

Radioisotopes emit subatomic particles that can be detected and tracked by imaging technologies. One of the most advanced uses of radioisotopes in medicine is the positron emission tomography (PET) scanner, which detects the activity in the body of a very small injection of radioactive glucose, the simple sugar that cells use for energy. The PET camera reveals to the medical team which of the patient's tissues are taking up the most glucose. Thus, the most metabolically active tissues show up as bright "hot spots" on the images (Figure 2.6). PET can reveal some cancerous masses because cancer cells consume glucose at a high rate to fuel their rapid reproduction.

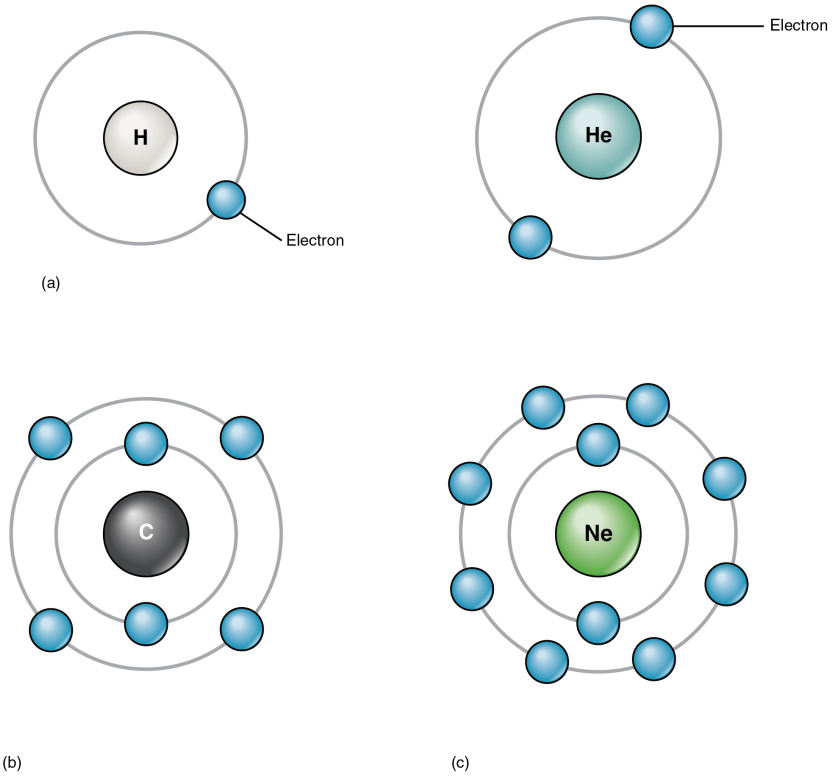


FIGURE 2.7 Electron Shells Electrons orbit the atomic nucleus at distinct levels of energy called electron shells. (a) With one electron, hydrogen only half-fills its electron shell. Helium also has a single shell, but its two electrons completely fill it. (b) The electrons of carbon completely fill its first electron shell, but only half-fills its second. (c) Neon, an element that does not occur in the body, has 10 electrons, filling both of its electron shells.

The factor that most strongly governs the tendency of an atom to participate in chemical reactions is the number of electrons in its valence shell. A **valence shell** is an atom's outermost electron shell. If the valence shell is full, the atom is stable; meaning its electrons are unlikely to be pulled away from the nucleus by the electrical charge of other atoms. If the valence shell is not full, the atom is reactive; meaning it will tend to react with other atoms in ways that make the valence shell full. Consider hydrogen, with its one electron only half-filling its valence shell. This single electron is likely to be drawn into relationships with the atoms of other elements, so that hydrogen's single valence shell can be stabilized.

All atoms (except hydrogen and helium with their single electron shells) are most stable when there are exactly eight electrons in their valence shell. This principle is referred to as the octet rule, and it states that an atom will give up, gain, or share electrons with another atom so that it ends up with eight electrons in its own valence shell. For example, oxygen, with six electrons in its valence shell, is likely to react with other atoms in a way that results in the addition of two electrons to oxygen's valence shell, bringing the number to eight. When two hydrogen atoms each share their single electron with oxygen, covalent bonds are formed, resulting in a molecule of water, H_2O.

In nature, atoms of one element tend to join with atoms of other elements in characteristic ways. For example, carbon commonly fills its valence shell by linking up with four atoms of hydrogen. In so doing, the two elements form the simplest of organic molecules, methane, which also is one of the most abundant and stable carbon-containing compounds on Earth. As stated above, another example is water; oxygen needs two electrons to fill its valence shell. It commonly interacts with two atoms of hydrogen, forming H_2O. Incidentally, the name "hydrogen" reflects its contribution to water (hydro- = "water"; -gen = "maker"). Thus, hydrogen is the "water maker."

Atoms that have more than one electron to donate or accept will end up with stronger positive or negative charges. A cation that has donated two electrons has a net charge of +2. Using magnesium (Mg) as an example, this can be written Mg^{++} or Mg^{2+}. An anion that has accepted two electrons has a net charge of –2. The ionic form of selenium (Se), for example, is typically written Se^{2-}.

The opposite charges of cations and anions exert a moderately strong mutual attraction that keeps the atoms in close proximity forming an ionic bond. An **ionic bond** is an ongoing, close association between ions of opposite charge. The table salt you sprinkle on your food owes its existence to ionic bonding. As shown in Figure 2.8, sodium commonly donates an electron to chlorine, becoming the cation Na^+. When chlorine accepts the electron, it becomes the chloride anion, Cl^-. With their opposing charges, these two ions strongly attract each other.

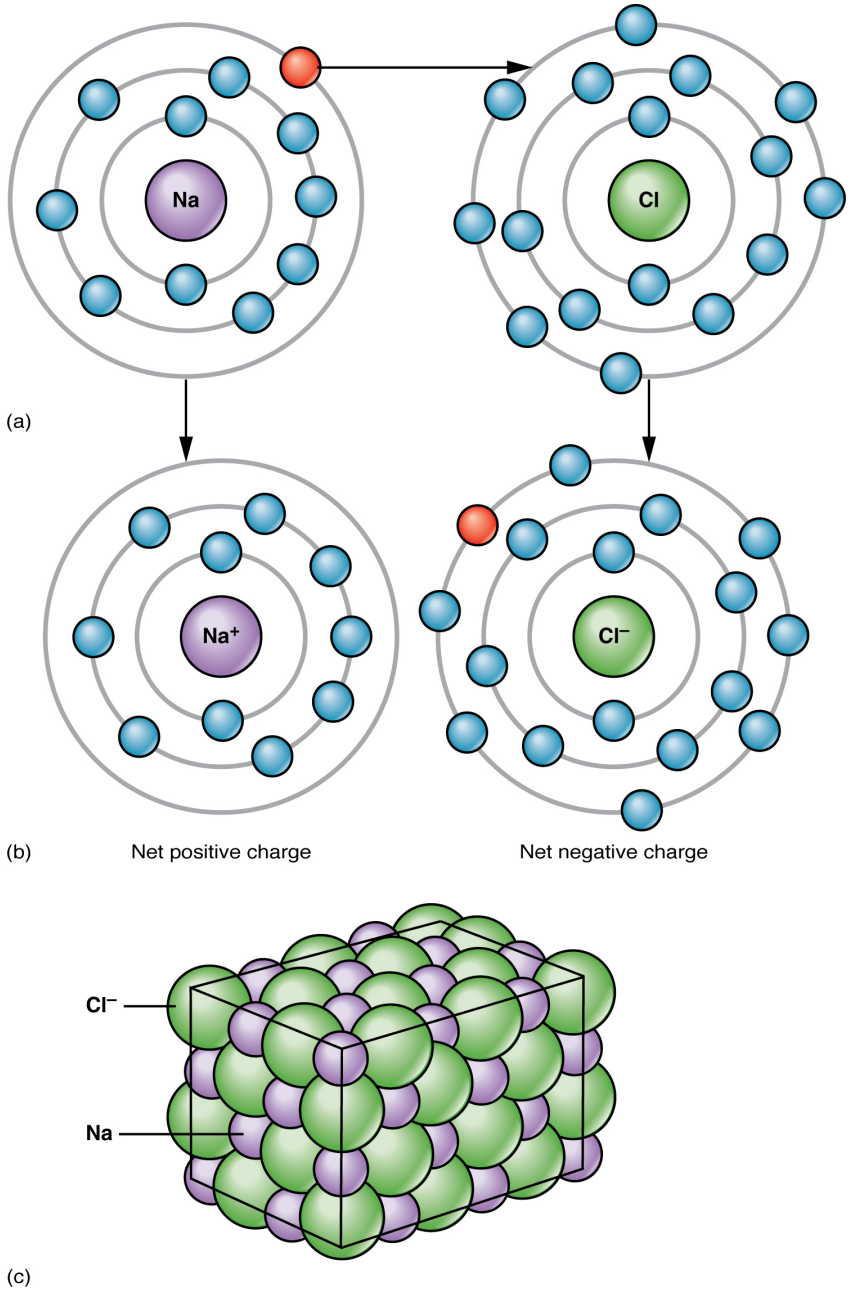
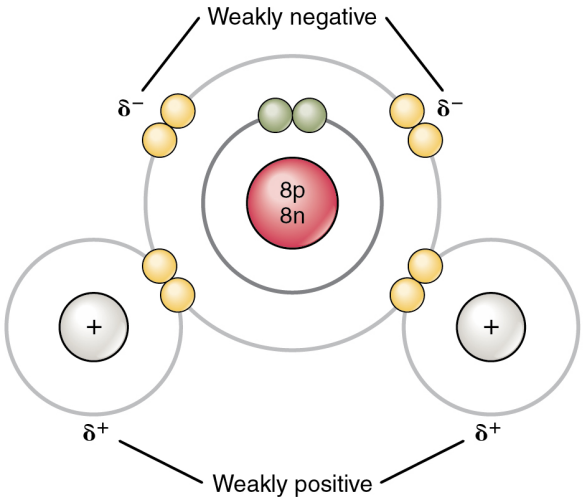


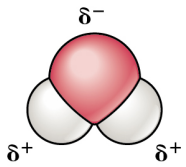
FIGURE 2.8 Ionic Bonding (a) Sodium readily donates the solitary electron in its valence shell to chlorine, which needs only one electron to have a full valence shell. (b) The opposite electrical charges of the resulting sodium cation and chloride anion result in the formation of a bond of attraction called an ionic bond. (c) The attraction of many sodium and chloride ions results in the formation of large groupings called crystals.

Water is an essential component of life because it is able to break the ionic bonds in salts to free the ions. In fact, in

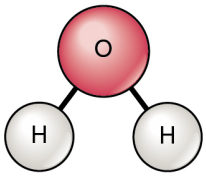
The most familiar example of a polar molecule is water (Figure 2.10). The molecule has three parts: one atom of oxygen, the nucleus of which contains eight protons, and two hydrogen atoms, whose nuclei each contain only one proton. Because every proton exerts an identical positive charge, a nucleus that contains eight protons exerts a charge eight times greater than a nucleus that contains one proton. This means that the negatively charged electrons present in the water molecule are more strongly attracted to the oxygen nucleus than to the hydrogen nuclei. Each hydrogen atom's single negative electron therefore migrates toward the oxygen atom, making the oxygen end of their bond slightly more negative than the hydrogen end of their bond.



(a) Planetary model of a water molecule



(b) Three-dimensional model of a water molecule



(c) Structural formula for water molecule

FIGURE 2.10 Polar Covalent Bonds in a Water Molecule

What is true for the bonds is true for the water molecule as a whole; that is, the oxygen region has a slightly negative charge and the regions of the hydrogen atoms have a slightly positive charge. These charges are often referred to as "partial charges" because the strength of the charge is less than one full electron, as would occur in an ionic bond. As shown in Figure 2.10, regions of weak polarity are indicated with the Greek letter delta (δ) and a plus (+) or minus (–) sign.

Even though a single water molecule is unimaginably tiny, it has mass, and the opposing electrical charges on the molecule pull that mass in such a way that it creates a shape somewhat like a triangular tent (see Figure 2.10**b**). This dipole, with the positive charges at one end formed by the hydrogen atoms at the "bottom" of the tent and the negative charge at the opposite end (the oxygen atom at the "top" of the tent) makes the charged regions highly likely to interact with charged regions of other polar molecules. For human physiology, the resulting bond is one of the most important formed by water—the hydrogen bond.

Hydrogen Bonds

A **hydrogen bond** is formed when a weakly positive hydrogen atom already bonded to one electronegative atom (for example, the oxygen in the water molecule) is attracted to another electronegative atom from another molecule. In other words, hydrogen bonds always include hydrogen that is already part of a polar molecule.

The most common example of hydrogen bonding in the natural world occurs between molecules of water. It happens before your eyes whenever two raindrops merge into a larger bead, or a creek spills into a river. Hydrogen bonding occurs because the weakly negative oxygen atom in one water molecule is attracted to the weakly positive

Chemical reactions that release more energy than they absorb are characterized as exergonic. The catabolism of the foods in your energy bar is an example. Some of the chemical energy stored in the bar is absorbed into molecules your body uses for fuel, but some of it is released—for example, as heat. In contrast, chemical reactions that absorb more energy than they release are endergonic. These reactions require energy input, and the resulting molecule stores not only the chemical energy in the original components, but also the energy that fueled the reaction. Because energy is neither created nor destroyed, where does the energy needed for endergonic reactions come from? In many cases, it comes from exergonic reactions.

Forms of Energy Important in Human Functioning

You have already learned that chemical energy is absorbed, stored, and released by chemical bonds. In addition to chemical energy, mechanical, radiant, and electrical energy are important in human functioning.

- Mechanical energy, which is stored in physical systems such as machines, engines, or the human body, directly powers the movement of matter. When you lift a brick into place on a wall, your muscles provide the mechanical energy that moves the brick.
- Radiant energy is energy emitted and transmitted as waves rather than matter. These waves vary in length from long radio waves and microwaves to short gamma waves emitted from decaying atomic nuclei. The full spectrum of radiant energy is referred to as the electromagnetic spectrum. The body uses the ultraviolet energy of sunlight to convert a compound in skin cells to vitamin D, which is essential to human functioning. The human eye evolved to see the wavelengths that comprise the colors of the rainbow, from red to violet, so that range in the spectrum is called "visible light."
- Electrical energy, supplied by electrolytes in cells and body fluids, contributes to the voltage changes that help transmit impulses in nerve and muscle cells.

Characteristics of Chemical Reactions

All chemical reactions begin with a **reactant**, the general term for the one or more substances that enter into the reaction. Sodium and chloride ions, for example, are the reactants in the production of table salt. The one or more substances produced by a chemical reaction are called the **product**.

In chemical reactions, the components of the reactants—the elements involved and the number of atoms of each—are all present in the product(s). Similarly, there is nothing present in the products that are not present in the reactants. This is because chemical reactions are governed by the law of conservation of mass, which states that matter cannot be created or destroyed in a chemical reaction.

Just as you can express mathematical calculations in equations such as 2 + 7 = 9, you can use chemical equations to show how reactants become products. As in math, chemical equations proceed from left to right, but instead of an equal sign, they employ an arrow or arrows indicating the direction in which the chemical reaction proceeds. For example, the chemical reaction in which one atom of nitrogen and three atoms of hydrogen produce ammonia would be written as $\mathrm{N} + 3\mathrm{H} \rightarrow \mathrm{NH_3}$. Correspondingly, the breakdown of ammonia into its components would be written as $\mathrm{NH_3} \rightarrow \mathrm{N} + 3\mathrm{H}$.

Notice that, in the first example, a nitrogen (N) atom and three hydrogen (H) atoms bond to form a compound. This anabolic reaction requires energy, which is then stored within the compound's bonds. Such reactions are referred to as synthesis reactions. A **synthesis reaction** is a chemical reaction that results in the synthesis (joining) of components that were formerly separate (Figure 2.12**a**). Again, nitrogen and hydrogen are reactants in a synthesis reaction that yields ammonia as the product. The general equation for a synthesis reaction is $\mathrm{A} + \mathrm{B} \rightarrow \mathrm{AB}$.

Concentration and Pressure

If just a few people are dancing at a club, they are unlikely to step on each other's toes. But as more and more people get up to dance—especially if the music is fast—collisions are likely to occur. It is the same with chemical reactions: the more particles present within a given space, the more likely those particles are to bump into one another. This means that chemists can speed up chemical reactions not only by increasing the **concentration** of particles—the number of particles in the space—but also by decreasing the volume of the space, which would correspondingly increase the pressure. If there were 100 dancers in that club, and the manager abruptly moved the party to a room half the size, the concentration of the dancers would double in the new space, and the likelihood of collisions would increase accordingly.

Enzymes and Other Catalysts

For two chemicals in nature to react with each other they first have to come into contact, and this occurs through random collisions. Because heat helps increase the kinetic energy of atoms, ions, and molecules, it promotes their collision. But in the body, extremely high heat—such as a very high fever—can damage body cells and be life-threatening. On the other hand, normal body temperature is not high enough to promote the chemical reactions that sustain life. That is where catalysts come in.

In chemistry, a **catalyst** is a substance that increases the rate of a chemical reaction without itself undergoing any change. You can think of a catalyst as a chemical change agent. They help increase the rate and force at which atoms, ions, and molecules collide, thereby increasing the probability that their valence shell electrons will interact.

The most important catalysts in the human body are enzymes. An **enzyme** is a catalyst composed of protein or ribonucleic acid (RNA), both of which will be discussed later in this chapter. Like all catalysts, enzymes work by lowering the level of energy that needs to be invested in a chemical reaction. A chemical reaction's **activation energy** is the "threshold" level of energy needed to break the bonds in the reactants. Once those bonds are broken, new arrangements can form. Without an enzyme to act as a catalyst, a much larger investment of energy is needed to ignite a chemical reaction (Figure 2.13).

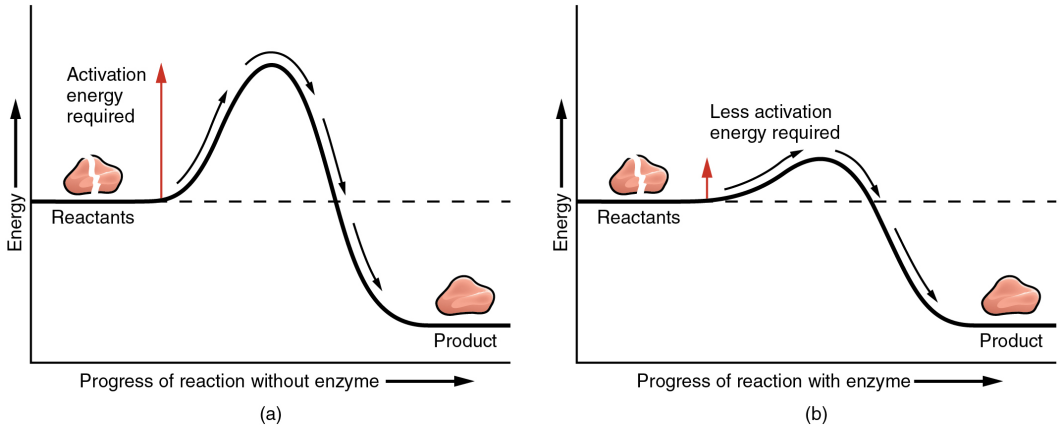


FIGURE 2.13 Enzymes Enzymes decrease the activation energy required for a given chemical reaction to occur. (a) Without an enzyme, the energy input needed for a reaction to begin is high. (b) With the help of an enzyme, less energy is needed for a reaction to begin.

Enzymes are critical to the body's healthy functioning. They assist, for example, with the breakdown of food and its conversion to energy. In fact, most of the chemical reactions in the body are facilitated by enzymes.

2.4 Inorganic Compounds Essential to Human Functioning

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare and contrast inorganic and organic compounds
- Identify the properties of water that make it essential to life
- Explain the role of salts in body functioning
- Distinguish between acids and bases, and explain their role in pH
- Discuss the role of buffers in helping the body maintain pH homeostasis

Water is certainly the most abundant solvent in the body; essentially all of the body's chemical reactions occur among compounds dissolved in water. Because water molecules are polar, with regions of positive and negative electrical charge, water readily dissolves ionic compounds and polar covalent compounds. Such compounds are referred to as hydrophilic, or "water-loving." As mentioned above, sugar dissolves well in water. This is because sugar molecules contain regions of hydrogen-oxygen polar bonds, making it hydrophilic. Nonpolar molecules, which do not readily dissolve in water, are called hydrophobic, or "water-fearing."

Concentrations of Solutes

Various mixtures of solutes and water are described in chemistry. The concentration of a given solute is the number of particles of that solute in a given space (oxygen makes up about 21 percent of atmospheric air). In the bloodstream of humans, glucose concentration is usually measured in milligram (mg) per deciliter (dL), and in a healthy adult averages about 100 mg/dL. Another method of measuring the concentration of a solute is by its molarity—which is moles (M) of the molecules per liter (L). The mole of an element is its atomic weight, while a mole of a compound is the sum of the atomic weights of its components, called the molecular weight. An often-used example is calculating a mole of glucose, with the chemical formula $C_6H_{12}O_6$. Using the periodic table, the atomic weight of carbon (C) is 12.011 grams (g), and there are six carbons in glucose, for a total atomic weight of 72.066 g. Doing the same calculations for hydrogen (H) and oxygen (O), the molecular weight equals 180.156g (the "gram molecular weight" of glucose). When water is added to make one liter of solution, you have one mole (1M) of glucose. This is particularly useful in chemistry because of the relationship of moles to "Avogadro's number." A mole of any solution has the same number of particles in it: 6.02×10^{23}. Many substances in the bloodstream and other tissue of the body are measured in thousandths of a mole, or millimoles (mM).

A **colloid** is a mixture that is somewhat like a heavy solution. The solute particles consist of tiny clumps of molecules large enough to make the liquid mixture opaque (because the particles are large enough to scatter light). Familiar examples of colloids are milk and cream. In the thyroid glands, the thyroid hormone is stored as a thick protein mixture also called a colloid.

A **suspension** is a liquid mixture in which a heavier substance is suspended temporarily in a liquid, but over time, settles out. This separation of particles from a suspension is called sedimentation. An example of sedimentation occurs in the blood test that establishes sedimentation rate, or sed rate. The test measures how quickly red blood cells in a test tube settle out of the watery portion of blood (known as plasma) over a set period of time. Rapid sedimentation of blood cells does not normally happen in the healthy body, but aspects of certain diseases can cause blood cells to clump together, and these heavy clumps of blood cells settle to the bottom of the test tube more quickly than do normal blood cells.

The Role of Water in Chemical Reactions

Two types of chemical reactions involve the creation or the consumption of water: dehydration synthesis and hydrolysis.

- In dehydration synthesis, one reactant gives up an atom of hydrogen and another reactant gives up a hydroxyl group (OH) in the synthesis of a new product. In the formation of their covalent bond, a molecule of water is released as a byproduct (Figure 2.14). This is also sometimes referred to as a condensation reaction.
- In hydrolysis, a molecule of water disrupts a compound, breaking its bonds. The water is itself split into H and OH. One portion of the severed compound then bonds with the hydrogen atom, and the other portion bonds with the hydroxyl group.

These reactions are reversible, and play an important role in the chemistry of organic compounds (which will be discussed shortly).

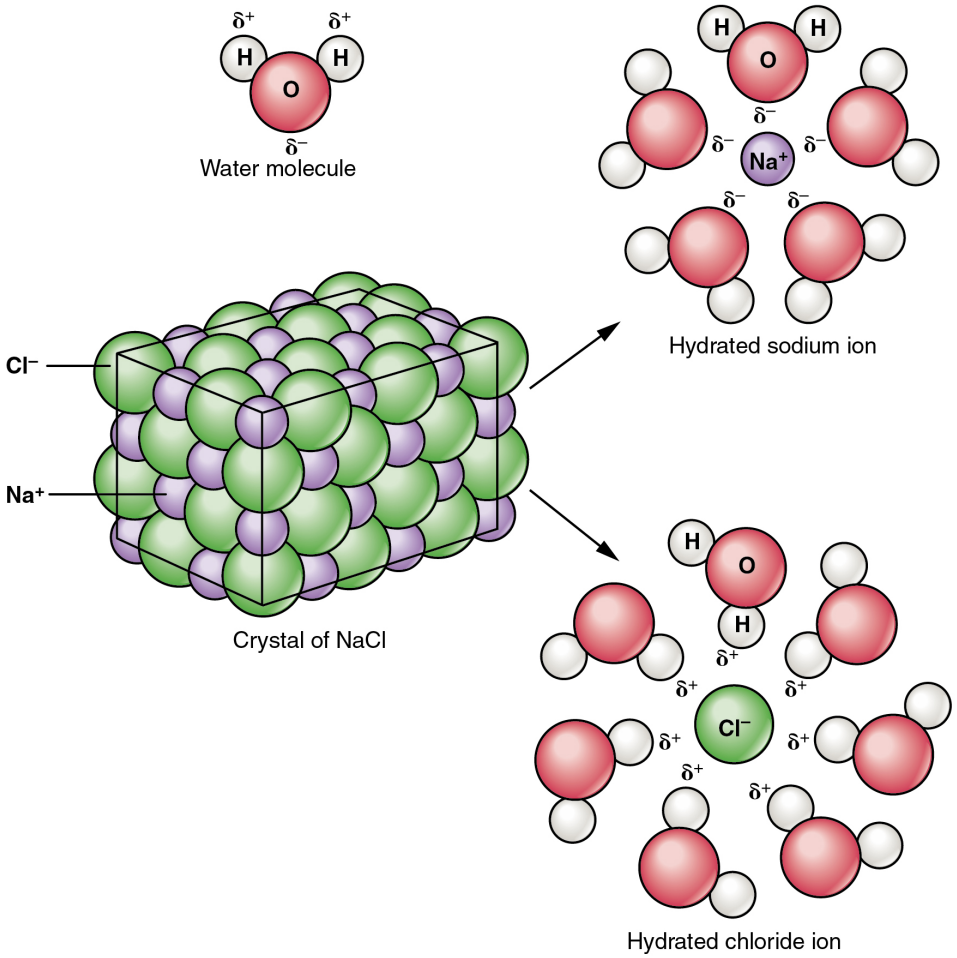


FIGURE 2.15 Dissociation of Sodium Chloride in Water Notice that the crystals of sodium chloride dissociate not into molecules of NaCl, but into Na^+ cations and Cl^- anions, each completely surrounded by water molecules.

Many other salts are important in the body. For example, bile salts produced by the liver help break apart dietary fats, and calcium phosphate salts form the mineral portion of teeth and bones.

Acids and Bases

Acids and bases, like salts, dissociate in water into electrolytes. Acids and bases can very much change the properties of the solutions in which they are dissolved.

Acids

An **acid** is a substance that releases hydrogen ions (H^+) in solution (Figure 2.16**a**). Because an atom of hydrogen has just one proton and one electron, a positively charged hydrogen ion is simply a proton. This solitary proton is highly likely to participate in chemical reactions. Strong acids are compounds that release all of their H^+ in solution; that is, they ionize completely. Hydrochloric acid (HCl), which is released from cells in the lining of the stomach, is a strong acid because it releases all of its H^+ in the stomach's watery environment. This strong acid aids in digestion and kills ingested microbes. Weak acids do not ionize completely; that is, some of their hydrogen ions remain bonded within a compound in solution. An example of a weak acid is vinegar, or acetic acid; it is called acetate after it gives up a proton.

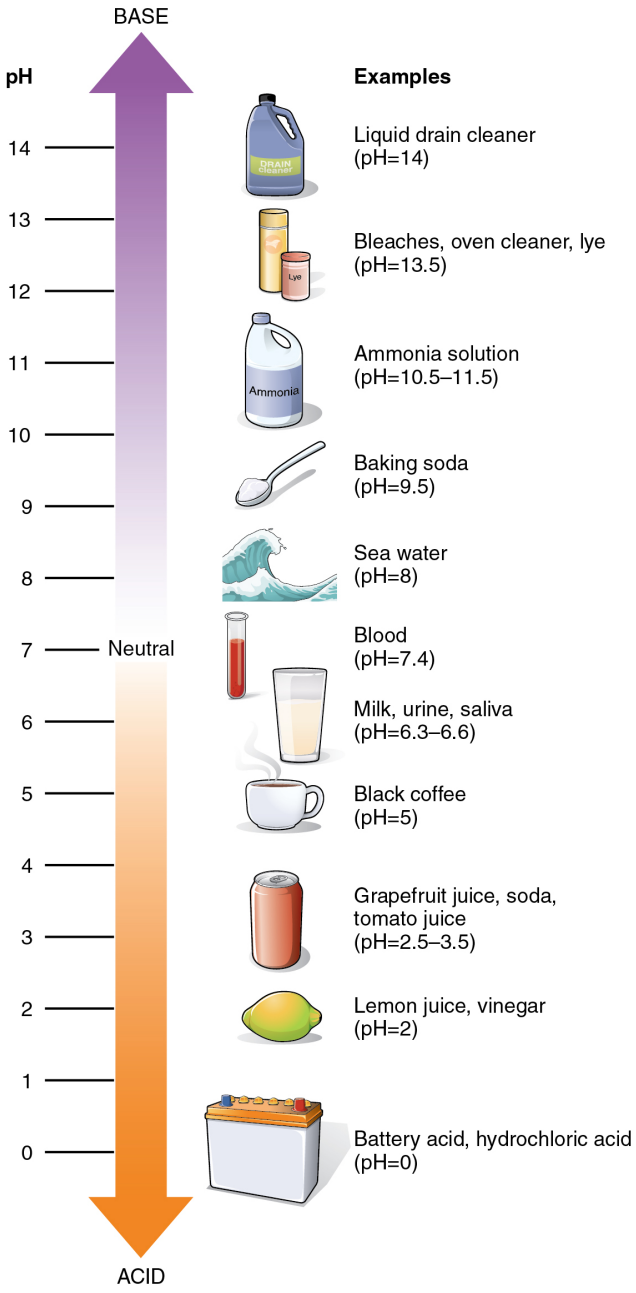


FIGURE 2.17 The pH Scale

Buffers

The pH of human blood normally ranges from 7.35 to 7.45, although it is typically identified as pH 7.4. At this slightly basic pH, blood can reduce the acidity resulting from the carbon dioxide (CO_2) constantly being released into the bloodstream by the trillions of cells in the body. Homeostatic mechanisms (along with exhaling CO_2 while breathing) normally keep the pH of blood within this narrow range. This is critical, because fluctuations—either too acidic or too alkaline—can lead to life-threatening disorders.

All cells of the body depend on homeostatic regulation of acid–base balance at a pH of approximately 7.4. The body therefore has several mechanisms for this regulation, involving breathing, the excretion of chemicals in urine, and the internal release of chemicals collectively called buffers into body fluids. A **buffer** is a solution of a weak acid and its conjugate base. A buffer can neutralize small amounts of acids or bases in body fluids. For example, if there is even a slight decrease below 7.35 in the pH of a bodily fluid, the buffer in the fluid—in this case, acting as a weak base—will bind the excess hydrogen ions. In contrast, if pH rises above 7.45, the buffer will act as a weak acid and contribute hydrogen ions.

and tending to function in chemical reactions as a single unit. You can think of functional groups as tightly knit "cliques" whose members are unlikely to be parted. Five functional groups are important in human physiology; these are the hydroxyl, carboxyl, amino, methyl and phosphate groups (Table 2.1).

Functional Groups Important in Human Physiology

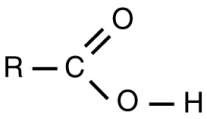
Functional group	Structural formula	Importance
Hydroxyl	—O—H	Hydroxyl groups are polar. They are components of all four types of organic compounds discussed in this chapter. They are involved in dehydration synthesis and hydrolysis reactions.
Carboxyl		Carboxyl groups are found within fatty acids, amino acids, and many other acids.
Amino	—N—H_2	Amino groups are found within amino acids, the building blocks of proteins.
Methyl	—C—H_3	Methyl groups are found within amino acids.
Phosphate	—P—O_4^{2-}	Phosphate groups are found within phospholipids and nucleotides.

TABLE 2.1

Carbon's affinity for covalent bonding means that many distinct and relatively stable organic molecules nevertheless readily form larger, more complex molecules. Any large molecule is referred to as **macromolecule** (macro- = "large"), and the organic compounds in this section all fit this description. However, some macromolecules are made up of several "copies" of single units called monomer (mono- = "one"; -mer = "part"). Like beads in a long necklace, these monomers link by covalent bonds to form long polymers (poly- = "many"). There are many examples of monomers and polymers among the organic compounds.

Monomers form polymers by engaging in dehydration synthesis (see Figure 2.14). As was noted earlier, this reaction results in the release of a molecule of water. Each monomer contributes: One gives up a hydrogen atom and the other gives up a hydroxyl group. Polymers are split into monomers by hydrolysis (-lysis = "rupture"). The bonds between their monomers are broken, via the donation of a molecule of water, which contributes a hydrogen atom to one monomer and a hydroxyl group to the other.

Carbohydrates

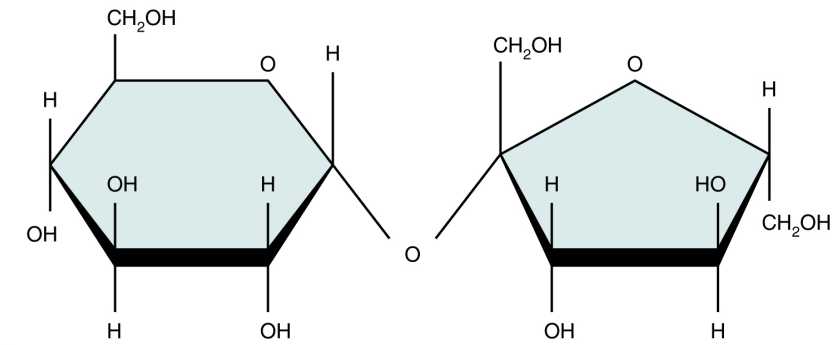
The term carbohydrate means "hydrated carbon." Recall that the root hydro- indicates water. A **carbohydrate** is a molecule composed of carbon, hydrogen, and oxygen; in most carbohydrates, hydrogen and oxygen are found in the same two-to-one relative proportions they have in water. In fact, the chemical formula for a "generic" molecule of carbohydrate is $(CH_2O)_n$.

Carbohydrates are referred to as saccharides, a word meaning "sugars." Three forms are important in the body. Monosaccharides are the monomers of carbohydrates. Disaccharides (di- = "two") are made up of two monomers. **Polysaccharides** are the polymers, and can consist of hundreds to thousands of monomers.

Monosaccharides

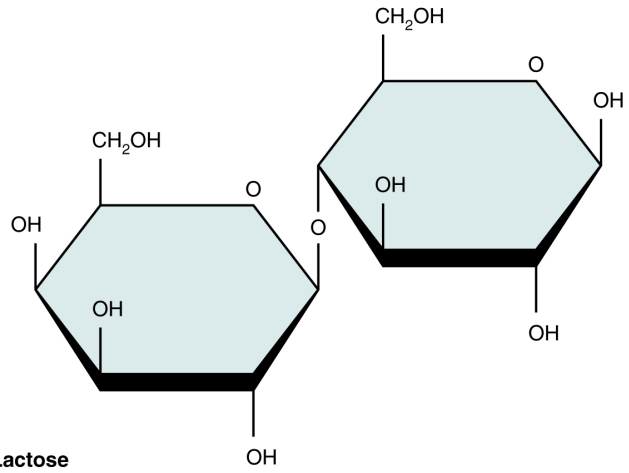
A **monosaccharide** is a monomer of carbohydrates. Five monosaccharides are important in the body. Three of these are the hexose sugars, so called because they each contain six atoms of carbon. These are glucose, fructose, and galactose, shown in Figure 2.18**a**. The remaining monosaccharides are the two pentose sugars, each of which contains five atoms of carbon. They are ribose and deoxyribose, shown in Figure 2.18**b**.

(a) The monosaccharides glucose and fructose bond to form sucrose



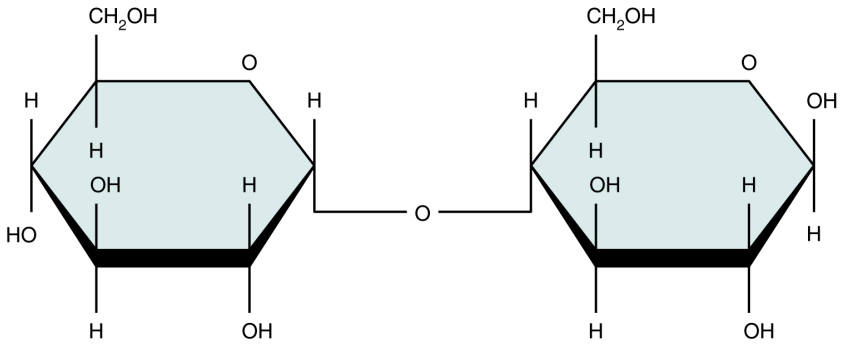
Sucrose

(b) The monosaccharides galactose and glucose bond to form lactose.



Lactose

(c) Two glucose monosaccharides bond to form maltose.



Maltose

FIGURE 2.19 Three Important Disaccharides All three important disaccharides form by dehydration synthesis.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/disaccharide) to observe the formation of a disaccharide. What happens when water encounters a glycosidic bond?

Polysaccharides

Polysaccharides can contain a few to a thousand or more monosaccharides. Three are important to the body (Figure 2.20):

- Starches are polymers of glucose. They occur in long chains called amylose or branched chains called amylopectin, both of which are stored in plant-based foods and are relatively easy to digest.

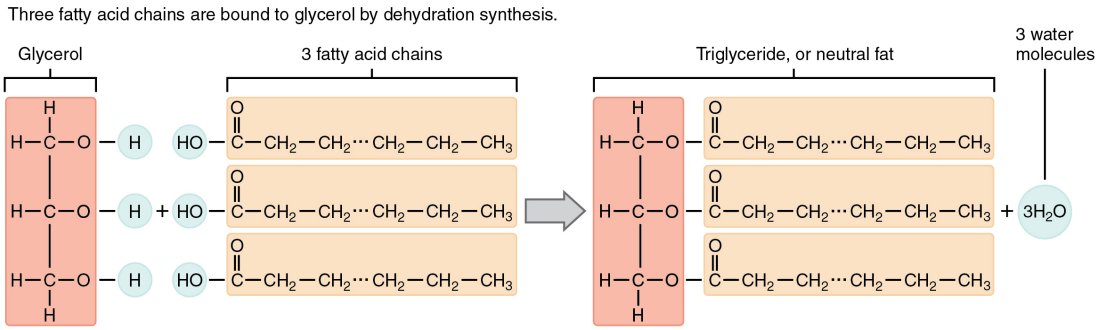


FIGURE 2.21 Triglycerides Triglycerides are composed of glycerol attached to three fatty acids via dehydration synthesis. Notice that glycerol gives up a hydrogen atom, and the carboxyl groups on the fatty acids each give up a hydroxyl group.

Triglycerides form via dehydration synthesis. Glycerol gives up hydrogen atoms from its hydroxyl groups at each bond, and the carboxyl group on each fatty acid chain gives up a hydroxyl group. A total of three water molecules are thereby released.

Fatty acid chains that have no double carbon bonds anywhere along their length and therefore contain the maximum number of hydrogen atoms are called saturated fatty acids. These straight, rigid chains pack tightly together and are solid or semi-solid at room temperature (Figure 2.22**a**). Butter and lard are examples, as is the fat found on a steak or in your own body. In contrast, fatty acids with one double carbon bond are kinked at that bond (Figure 2.22**b**). These monounsaturated fatty acids are therefore unable to pack together tightly, and are liquid at room temperature. Polyunsaturated fatty acids contain two or more double carbon bonds, and are also liquid at room temperature. Plant oils such as olive oil typically contain both mono- and polyunsaturated fatty acids.

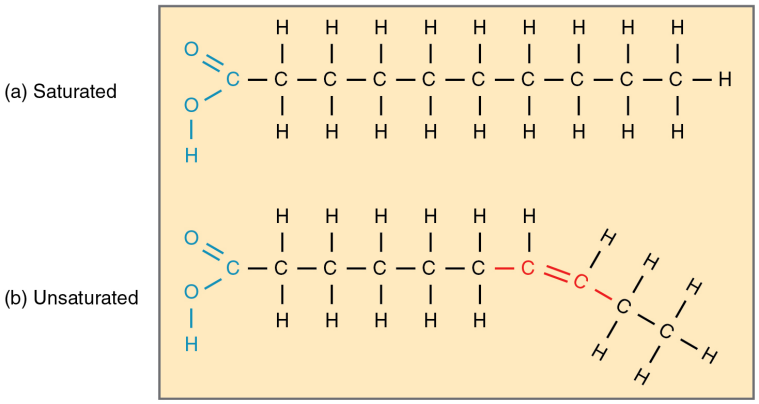


FIGURE 2.22 Fatty Acid Shapes The level of saturation of a fatty acid affects its shape. (a) Saturated fatty acid chains are straight. (b) Unsaturated fatty acid chains are kinked.

Whereas a diet high in saturated fatty acids increases the risk of heart disease, a diet high in unsaturated fatty acids is thought to reduce the risk. This is especially true for the omega-3 unsaturated fatty acids found in cold-water fish such as salmon. These fatty acids have their first double carbon bond at the third hydrocarbon from the methyl group (referred to as the omega end of the molecule).

Finally, *trans* fatty acids found in some processed foods, including some stick and tub margarines, are thought to be even more harmful to the heart and blood vessels than saturated fatty acids. *Trans* fats are created from unsaturated fatty acids (such as corn oil) when chemically treated to produce partially hydrogenated fats.

As a group, triglycerides are a major fuel source for the body. When you are resting or asleep, a majority of the energy used to keep you alive is derived from triglycerides stored in your fat (adipose) tissues. Triglycerides also fuel long, slow physical activity such as gardening or hiking, and contribute a modest percentage of energy for vigorous physical activity. Dietary fat also assists the absorption and transport of the nonpolar fat-soluble vitamins A, D, E, and K. Additionally, stored body fat protects and cushions the body's bones and internal organs, and acts as insulation to retain body heat.

Fatty acids are also components of glycolipids, which are sugar-fat compounds found in the cell membrane. Lipoproteins are compounds in which the hydrophobic triglycerides are packaged in protein envelopes for transport

of other atoms and molecules (see Figure 2.23**b**). Although both plants and animals synthesize sterols, the type that makes the most important contribution to human structure and function is cholesterol, which is synthesized by the liver in humans and animals and is also present in most animal-based foods. Like other lipids, cholesterol's hydrocarbons make it hydrophobic; however, it has a polar hydroxyl head that is hydrophilic. Cholesterol is an important component of bile acids, compounds that help emulsify dietary fats. In fact, the word root chole- refers to bile. Cholesterol is also a building block of many hormones, signaling molecules that the body releases to regulate processes at distant sites. Finally, like phospholipids, cholesterol molecules are found in the cell membrane, where their hydrophobic and hydrophilic regions help regulate the flow of substances into and out of the cell.

Prostaglandins

Like a hormone, a **prostaglandin** is one of a group of signaling molecules, but prostaglandins are derived from unsaturated fatty acids (see Figure 2.23**c**). One reason that the omega-3 fatty acids found in fish are beneficial is that they stimulate the production of certain prostaglandins that help regulate aspects of blood pressure and inflammation, and thereby reduce the risk for heart disease. Prostaglandins also sensitize nerves to pain. One class of pain-relieving medications called nonsteroidal anti-inflammatory drugs (NSAIDs) works by reducing the effects of prostaglandins.

Proteins

You might associate proteins with muscle tissue, but in fact, proteins are critical components of all tissues and organs. A **protein** is an organic molecule composed of amino acids linked by peptide bonds. Proteins include the keratin in the epidermis of skin that protects underlying tissues, the collagen found in the dermis of skin, in bones, and in the meninges that cover the brain and spinal cord. Proteins are also components of many of the body's functional chemicals, including digestive enzymes in the digestive tract, antibodies, the neurotransmitters that neurons use to communicate with other cells, and the peptide-based hormones that regulate certain body functions (for instance, growth hormone). While carbohydrates and lipids are composed of hydrocarbons and oxygen, all proteins also contain nitrogen (N), and many contain sulfur (S), in addition to carbon, hydrogen, and oxygen.

Microstructure of Proteins

Proteins are polymers made up of nitrogen-containing monomers called amino acids. An **amino acid** is a molecule composed of an amino group and a carboxyl group, together with a variable side chain. Just 20 different amino acids contribute to nearly all of the thousands of different proteins important in human structure and function. Body proteins contain a unique combination of a few dozen to a few hundred of these 20 amino acid monomers. All 20 of these amino acids share a similar structure (Figure 2.24). All consist of a central carbon atom to which the following are bonded:

- a hydrogen atom
- an alkaline (basic) amino group NH_2 (see Table 2.1)
- an acidic carboxyl group COOH (see Table 2.1)
- a variable group

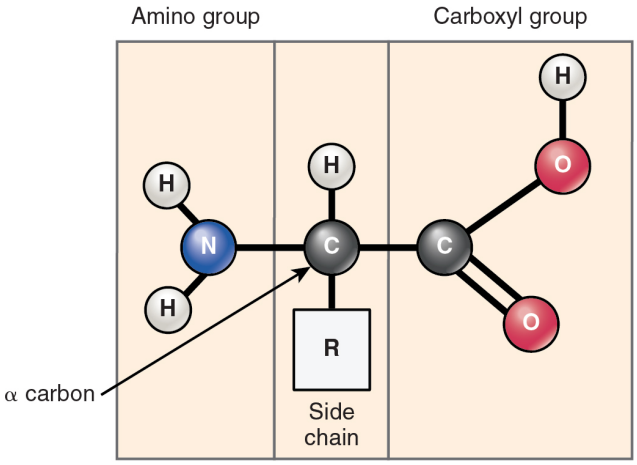


FIGURE 2.24 Structure of an Amino Acid

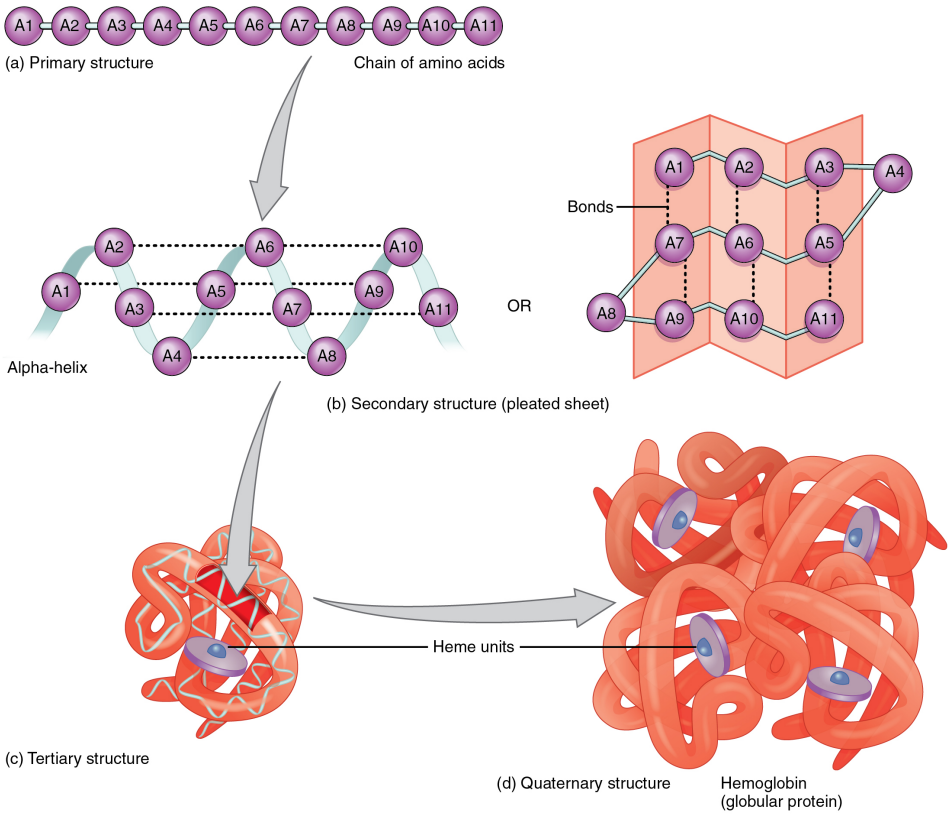


FIGURE 2.26 The Shape of Proteins (a) The primary structure is the sequence of amino acids that make up the polypeptide chain. (b) The secondary structure, which can take the form of an alpha-helix or a beta-pleated sheet, is maintained by hydrogen bonds between amino acids in different regions of the original polypeptide strand. (c) The tertiary structure occurs as a result of further folding and bonding of the secondary structure. (d) The quaternary structure occurs as a result of interactions between two or more tertiary subunits. The example shown here is hemoglobin, a protein in red blood cells which transports oxygen to body tissues.

Although some polypeptides exist as linear chains, most are twisted or folded into more complex secondary structures that form when bonding occurs between amino acids with different properties at different regions of the polypeptide. The most common secondary structure is a spiral called an alpha-helix. If you were to take a length of string and simply twist it into a spiral, it would not hold the shape. Similarly, a strand of amino acids could not maintain a stable spiral shape without the help of hydrogen bonds, which create bridges between different regions of the same strand (see Figure 2.26**b**). Less commonly, a polypeptide chain can form a beta-pleated sheet, in which hydrogen bonds form bridges between different regions of a single polypeptide that has folded back upon itself, or between two or more adjacent polypeptide chains.

The secondary structure of proteins further folds into a compact three-dimensional shape, referred to as the protein's tertiary structure (see Figure 2.26**c**). In this configuration, amino acids that had been very distant in the primary chain can be brought quite close via hydrogen bonds or, in proteins containing cysteine, via disulfide bonds. A **disulfide bond** is a covalent bond between sulfur atoms in a polypeptide. Often, two or more separate polypeptides bond to form an even larger protein with a quaternary structure (see Figure 2.26**d**). The polypeptide subunits forming a quaternary structure can be identical or different. For instance, hemoglobin, the protein found in red blood cells is composed of four tertiary polypeptides, two of which are called alpha chains and two of which are called beta chains.

When they are exposed to extreme heat, acids, bases, and certain other substances, proteins will denature. **Denaturation** is a change in the structure of a molecule through physical or chemical means. Denatured proteins lose their functional shape and are no longer able to carry out their jobs. An everyday example of protein denaturation is the curdling of milk when acidic lemon juice is added.

The contribution of the shape of a protein to its function can hardly be exaggerated. For example, the long, slender shape of protein strands that make up muscle tissue is essential to their ability to contract (shorten) and relax (lengthen). As another example, bones contain long threads of a protein called collagen that acts as scaffolding

concentration of proteins in the blood, the cells, and the spaces between cells helps ensure a balance of fluids in these various "compartments." Moreover, proteins in the cell membrane help to transport electrolytes in and out of the cell, keeping these ions in a healthy balance. Like lipids, proteins can bind with carbohydrates. They can thereby produce glycoproteins or proteoglycans, both of which have many functions in the body.

The body can use proteins for energy when carbohydrate and fat intake is inadequate, and stores of glycogen and adipose tissue become depleted. However, since there is no storage site for protein except functional tissues, using protein for energy causes tissue breakdown, and results in body wasting.

Nucleotides

The fourth type of organic compound important to human structure and function are the nucleotides (Figure 2.28). A **nucleotide** is one of a class of organic compounds composed of three subunits:

- one or more phosphate groups
- a pentose sugar: either deoxyribose or ribose
- a nitrogen-containing base: adenine, cytosine, guanine, thymine, or uracil

Nucleotides can be assembled into nucleic acids (DNA or RNA) or the energy compound adenosine triphosphate.

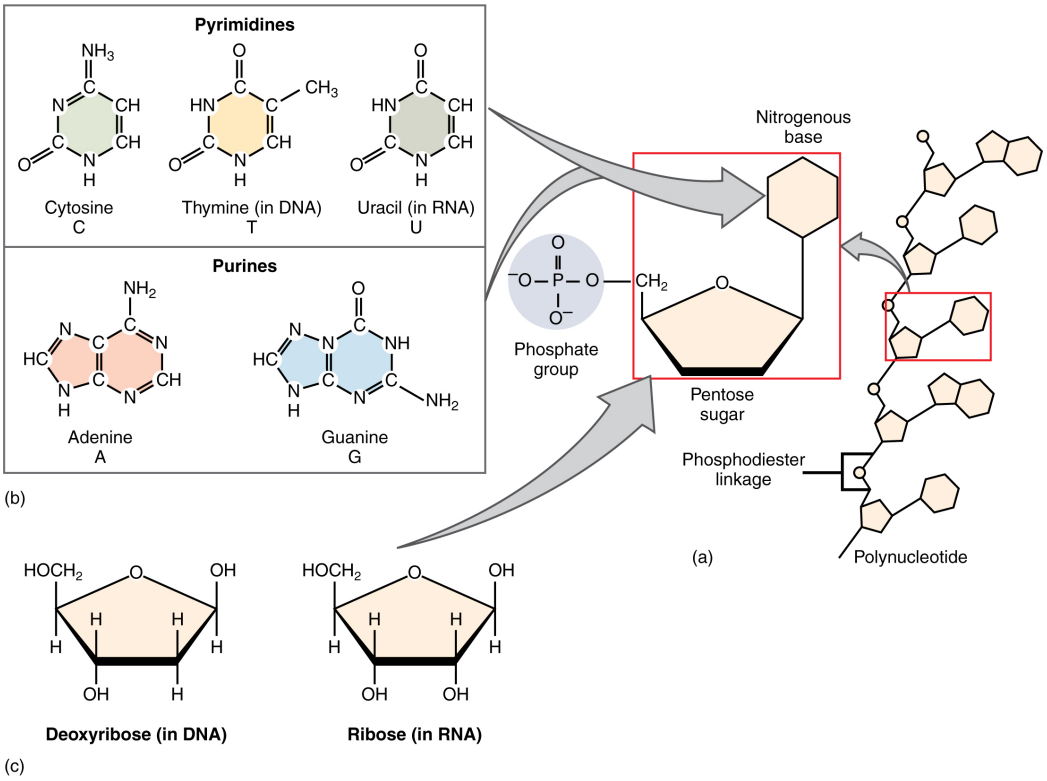


FIGURE 2.28 Nucleotides (a) The building blocks of all nucleotides are one or more phosphate groups, a pentose sugar, and a nitrogen-containing base. (b) The nitrogen-containing bases of nucleotides. (c) The two pentose sugars of DNA and RNA.

Nucleic Acids

The nucleic acids differ in their type of pentose sugar. **Deoxyribonucleic acid (DNA)** is nucleotide that stores genetic information. DNA contains deoxyribose (so-called because it has one less atom of oxygen than ribose) plus one phosphate group and one nitrogen-containing base. The "choices" of base for DNA are adenine, cytosine, guanine, and thymine. **Ribonucleic acid (RNA)** is a ribose-containing nucleotide that helps manifest the genetic code as protein. RNA contains ribose, one phosphate group, and one nitrogen-containing base, but the "choices" of base for RNA are adenine, cytosine, guanine, and uracil.

The nitrogen-containing bases adenine and guanine are classified as purines. A **purine** is a nitrogen-containing molecule with a double ring structure, which accommodates several nitrogen atoms. The bases cytosine, thymine (found in DNA only) and uracil (found in RNA only) are pyramidines. A **pyramidine** is a nitrogen-containing base with

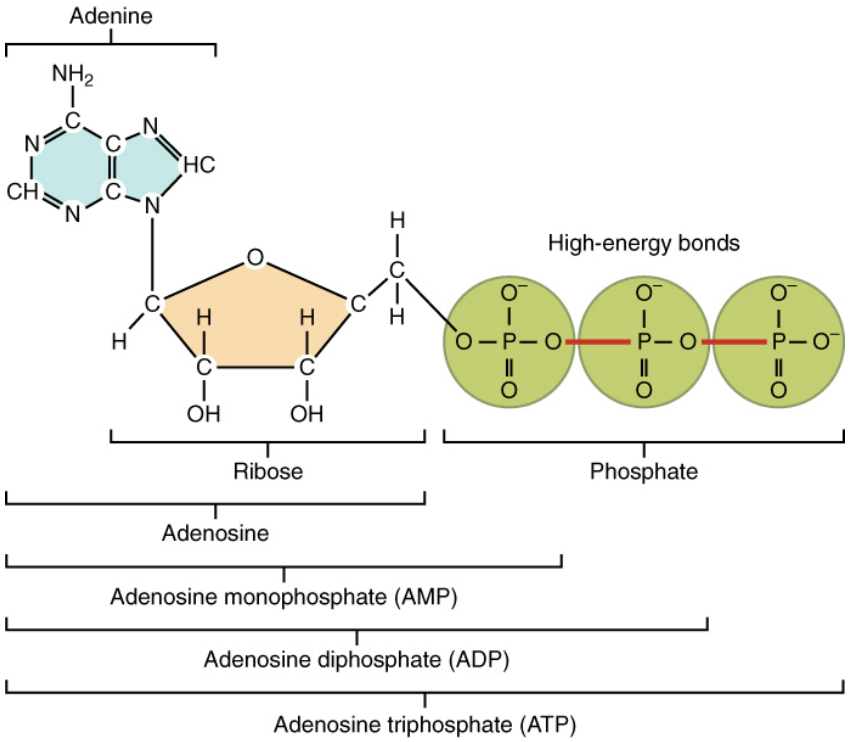


FIGURE 2.30 **Structure of Adenosine Triphosphate (ATP)**

When a phosphate group is cleaved from ATP, the products are adenosine diphosphate (ADP) and inorganic phosphate (P_i). This hydrolysis reaction can be written:

$$\mathrm{ATP} + \mathrm{H_2O} \rightarrow \mathrm{ADP} + \mathrm{P_i} + \text{energy}$$

Removal of a second phosphate leaves adenosine monophosphate (AMP) and two phosphate groups. Again, these reactions also liberate the energy that had been stored in the phosphate-phosphate bonds. They are reversible, too, as when ADP undergoes phosphorylation. **Phosphorylation** is the addition of a phosphate group to an organic compound, in this case, resulting in ATP. In such cases, the same level of energy that had been released during hydrolysis must be reinvested to power dehydration synthesis.

Cells can also transfer a phosphate group from ATP to another organic compound. For example, when glucose first enters a cell, a phosphate group is transferred from ATP, forming glucose phosphate ($C_6H_{12}O_6$—P) and ADP. Once glucose is phosphorylated in this way, it can be stored as glycogen or metabolized for immediate energy.

periodic table of the elements arrangement of the elements in a table according to their atomic number; elements having similar properties because of their electron arrangements compose columns in the table, while elements having the same number of valence shells compose rows in the table

pH negative logarithm of the hydrogen ion (H^+) concentration of a solution

phospholipid a lipid compound in which a phosphate group is combined with a diglyceride

phosphorylation addition of one or more phosphate groups to an organic compound

polar molecule molecule with regions that have opposite charges resulting from uneven numbers of electrons in the nuclei of the atoms participating in the covalent bond

polysaccharide compound consisting of more than two carbohydrate monomers bonded by dehydration synthesis via glycosidic bonds

potential energy stored energy matter possesses because of the positioning or structure of its components

product one or more substances produced by a chemical reaction

prostaglandin lipid compound derived from fatty acid chains and important in regulating several body processes

protein class of organic compounds that are composed of many amino acids linked together by peptide bonds

proton heavy subatomic particle having a positive charge and found in the atom's nucleus

purine nitrogen-containing base with a double ring structure; adenine and guanine

pyrimidine nitrogen-containing base with a single ring structure; cytosine, thiamine, and uracil

radioactive isotope unstable, heavy isotope that gives off subatomic particles, or electromagnetic energy, as it decays; also called radioisotopes

reactant one or more substances that enter into the reaction

ribonucleic acid (RNA) ribose-containing nucleotide that helps manifest the genetic code as protein

solution homogeneous liquid mixture in which a solute is dissolved into molecules within a solvent

steroid (also, sterol) lipid compound composed of four hydrocarbon rings bonded to a variety of other atoms and molecules

substrate reactant in an enzymatic reaction

suspension liquid mixture in which particles distributed in the liquid settle out over time

synthesis reaction type of anabolic reaction in which two or more atoms or molecules bond, resulting in the formation of a larger molecule

triglyceride lipid compound composed of a glycerol molecule bonded with three fatty acid chains

valence shell outermost electron shell of an atom

Chapter Review

2.1 Elements and Atoms: The Building Blocks of Matter

The human body is composed of elements, the most abundant of which are oxygen (O), carbon (C), hydrogen (H) and nitrogen (N). You obtain these elements from the foods you eat and the air you breathe. The smallest unit of an element that retains all of the properties of that element is an atom. But, atoms themselves contain many subatomic particles, the three most important of which are protons, neutrons, and electrons. These particles do not vary in quality from one element to another; rather, what gives an element its distinctive identification is the quantity of its protons, called its atomic number. Protons and neutrons contribute nearly all of an atom's mass; the number of protons and neutrons is an element's mass number. Heavier and lighter versions of the same element can occur in nature because these versions have different numbers of neutrons. Different versions of an element are called isotopes.

The tendency of an atom to be stable or to react readily with other atoms is largely due to the behavior of the electrons within the atom's outermost electron shell, called its valence shell. Helium, as well as larger atoms with eight electrons in their valence shell, is unlikely to participate in chemical reactions because they are stable. All other atoms tend to accept, donate, or share electrons in a process that brings the electrons in their valence shell to eight (or in the case of hydrogen, to two).

2.2 Chemical Bonds

Each moment of life, atoms of oxygen, carbon, hydrogen, and the other elements of the human body are making and breaking chemical bonds. Ions are charged atoms that form when an atom donates or accepts one or more negatively charged electrons. Cations (ions with a positive charge) are attracted to anions (ions with a negative charge). This attraction is called an ionic bond. In covalent bonds, the participating atoms do not lose or gain electrons, but rather share them. Molecules with nonpolar covalent bonds are electrically balanced, and have a linear

Nucleotides are compounds with three building blocks: one or more phosphate groups, a pentose sugar, and a nitrogen-containing base. DNA and RNA are nucleic acids that function in protein synthesis. ATP is the body's fundamental molecule of energy transfer. Removal or addition of phosphates releases or invests energy.

Interactive Link Questions

1. Visit this website (http://openstax.org/l/ptable) to view the periodic table. In the periodic table of the elements, elements in a single column have the same number of electrons that can participate in a chemical reaction. These electrons are known as "valence electrons." For example, the elements in the first column all have a single valence electron—an electron that can be "donated" in a chemical reaction with another atom. What is the meaning of a mass number shown in parentheses?

2. Visit this website (http://openstax.org/l/electenergy) to learn about electrical energy and the attraction/repulsion of charges. What happens to the charged electroscope when a conductor is moved between its plastic sheets, and why?

3. Watch this video (http://openstax.org/l/disaccharide) to observe the formation of a disaccharide. What happens when water encounters a glycosidic bond?

Review Questions

4. Together, just four elements make up more than 95 percent of the body's mass. These include _____.
- a. calcium, magnesium, iron, and carbon
- b. oxygen, calcium, iron, and nitrogen
- c. sodium, chlorine, carbon, and hydrogen
- d. oxygen, carbon, hydrogen, and nitrogen

5. The smallest unit of an element that still retains the distinctive behavior of that element is an _____.
- a. electron
- b. atom
- c. elemental particle
- d. isotope

6. The characteristic that gives an element its distinctive properties is its number of _____.
- a. protons
- b. neutrons
- c. electrons
- d. atoms

7. On the periodic table of the elements, mercury (Hg) has an atomic number of 80 and a mass number of 200.59. It has seven stable isotopes. The most abundant of these probably have _____.
- a. about 80 neutrons each
- b. fewer than 80 neutrons each
- c. more than 80 neutrons each
- d. more electrons than neutrons

8. Nitrogen has an atomic number of seven. How many electron shells does it likely have?
- a. one
- b. two
- c. three
- d. four

9. Which of the following is a molecule, but *not* a compound?
- a. H_2O
- b. ^2H
- c. H_2
- d. H^+

10. A molecule of ammonia contains one atom of nitrogen and three atoms of hydrogen. These are linked with _____.
- a. ionic bonds
- b. nonpolar covalent bonds
- c. polar covalent bonds
- d. hydrogen bonds

11. When an atom donates an electron to another atom, it becomes
- a. an ion
- b. an anion
- c. nonpolar
- d. all of the above

12. A substance formed of crystals of equal numbers of cations and anions held together by ionic bonds is called a(n) _____.
- a. noble gas
- b. salt
- c. electrolyte
- d. dipole

27. Which of the following is a functional group that is part of a building block of proteins?
   a. phosphate
   b. adenine
   c. amino
   d. ribose

28. A pentose sugar is a part of the monomer used to build which type of macromolecule?
   a. polysaccharides
   b. nucleic acids
   c. phosphorylated glucose
   d. glycogen

29. A phospholipid _____.
   a. has both polar and nonpolar regions
   b. is made up of a triglyceride bonded to a phosphate group
   c. is a building block of ATP
   d. can donate both cations and anions in solution

30. In DNA, nucleotide bonding forms a compound with a characteristic shape known as a(n) _____.
   a. beta chain
   b. pleated sheet
   c. alpha helix
   d. double helix

31. Uracil _____.
   a. contains nitrogen
   b. is a pyrimidine
   c. is found in RNA
   d. all of the above

32. The ability of an enzyme's active sites to bind only substrates of compatible shape and charge is known as _____.
   a. selectivity
   b. specificity
   c. subjectivity
   d. specialty

Critical Thinking Questions

33. The most abundant elements in the foods and beverages you consume are oxygen, carbon, hydrogen, and nitrogen. Why might having these elements in consumables be useful?

34. Oxygen, whose atomic number is eight, has three stable isotopes: ^{16}O, ^{17}O, and ^{18}O. Explain what this means in terms of the number of protons and neutrons.

35. Magnesium is an important element in the human body, especially in bones. Magnesium's atomic number is 12. Is it stable or reactive? Why? If it were to react with another atom, would it be more likely to accept or to donate one or more electrons?

36. Explain why CH_4 is one of the most common molecules found in nature. Are the bonds between the atoms ionic or covalent?

37. In a hurry one day, you merely rinse your lunch dishes with water. As you are drying your salad bowl, you notice that it still has an oily film. Why was the water alone not effective in cleaning the bowl?

38. Could two atoms of oxygen engage in ionic bonding? Why or why not?

39. $AB + CD \rightarrow AD + BE$ Is this a legitimate example of an exchange reaction? Why or why not?

40. When you do a load of laundry, why do you not just drop a bar of soap into the washing machine? In other words, why is laundry detergent sold as a liquid or powder?

41. The pH of lemon juice is 2, and the pH of orange juice is 4. Which of these is more acidic, and by how much? What does this mean?

42. During a party, Eli loses a bet and is forced to drink a bottle of lemon juice. Not long thereafter, he begins complaining of having difficulty breathing, and his friends take him to the local emergency room. There, he is given an intravenous solution of bicarbonate. Why?

43. If the disaccharide maltose is formed from two glucose monosaccharides, which are hexose sugars, how many atoms of carbon, hydrogen, and oxygen does maltose contain and why?

44. Once dietary fats are digested and absorbed, why can they not be released directly into the bloodstream?

introduced to the various types of cells in the body.

A primary responsibility of each cell is to contribute to homeostasis. Homeostasis is a term used in biology that refers to a dynamic state of balance within parameters that are compatible with life. For example, living cells require a water-based environment to survive in, and there are various physical (anatomical) and physiological mechanisms that keep all of the trillions of living cells in the human body moist. This is one aspect of homeostasis. When a particular parameter, such as blood pressure or blood oxygen content, moves far enough *out* of homeostasis (generally becoming too high or too low), illness or disease—and sometimes death—inevitably results.

The concept of a cell started with microscopic observations of dead cork tissue by scientist Robert Hooke in 1665. Without realizing their function or importance, Hook coined the term "cell" based on the resemblance of the small subdivisions in the cork to the rooms that monks inhabited, called cells. About ten years later, Antonie van Leeuwenhoek became the first person to observe living and moving cells under a microscope. In the century that followed, the theory that cells represented the basic unit of life would develop. These tiny fluid-filled sacs house components responsible for the thousands of biochemical reactions necessary for an organism to grow and survive. In this chapter, you will learn about the major components and functions of a prototypical, generalized cell and discover some of the different types of cells in the human body.

3.1 The Cell Membrane

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the molecular components that make up the cell membrane
- Explain the major features and properties of the cell membrane
- Differentiate between materials that can and cannot diffuse through the lipid bilayer
- Compare and contrast different types of passive transport with active transport, providing examples of each

Despite differences in structure and function, all living cells in multicellular organisms have a surrounding cell membrane. As the outer layer of your skin separates your body from its environment, the cell membrane (also known as the plasma membrane) separates the inner contents of a cell from its exterior environment. This cell membrane provides a protective barrier around the cell and regulates which materials can pass in or out.

Structure and Composition of the Cell Membrane

The **cell membrane** is an extremely pliable structure composed primarily of back-to-back phospholipids (a "bilayer"). Cholesterol is also present, which contributes to the fluidity of the membrane, and there are various proteins embedded within the membrane that have a variety of functions.

A single phospholipid molecule has a phosphate group on one end, called the "head," and two side-by-side chains of fatty acids that make up the lipid tails (Figure 3.2). The phosphate group is negatively charged, making the head polar and hydrophilic—or "water loving." A **hydrophilic** molecule (or region of a molecule) is one that is attracted to water. The phosphate heads are thus attracted to the water molecules of both the extracellular and intracellular environments. The lipid tails, on the other hand, are uncharged, or nonpolar, and are hydrophobic—or "water fearing." A **hydrophobic** molecule (or region of a molecule) repels and is repelled by water. Some lipid tails consist of saturated fatty acids and some contain unsaturated fatty acids. This combination adds to the fluidity of the tails that are constantly in motion. Phospholipids are thus amphipathic molecules. An **amphipathic** molecule is one that contains both a hydrophilic and a hydrophobic region. In fact, soap works to remove oil and grease stains because it has amphipathic properties. The hydrophilic portion can dissolve in water while the hydrophobic portion can trap grease in micelles that then can be washed away.

as certain ions, to pass into or out of the cell.

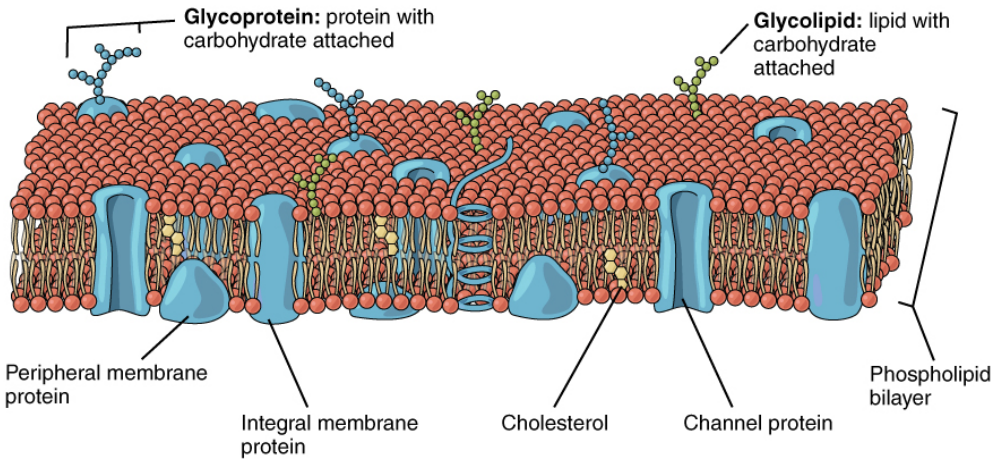


FIGURE 3.4 Cell Membrane The cell membrane of the cell is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol, some with carbohydrate groups attached.

Another important group of integral proteins are cell recognition proteins, which serve to mark a cell's identity so that it can be recognized by other cells. A **receptor** is a type of recognition protein that can selectively bind a specific molecule outside the cell, and this binding induces a chemical reaction within the cell. A **ligand** is the specific molecule that binds to and activates a receptor. Some integral proteins serve dual roles as both a receptor and an ion channel. One example of a receptor-ligand interaction is the receptors on nerve cells that bind neurotransmitters, such as dopamine. When a dopamine molecule binds to a dopamine receptor protein, a channel within the transmembrane protein opens to allow certain ions to flow into the cell.

Some integral membrane proteins are glycoproteins. A **glycoprotein** is a protein that has carbohydrate molecules attached, which extend into the extracellular matrix. The attached carbohydrate tags on glycoproteins aid in cell recognition. The carbohydrates that extend from membrane proteins and even from some membrane lipids collectively form the glycocalyx. The **glycocalyx** is a fuzzy-appearing coating around the cell formed from glycoproteins and other carbohydrates attached to the cell membrane. The glycocalyx can have various roles. For example, it may have molecules that allow the cell to bind to another cell, it may contain receptors for hormones, or it might have enzymes to break down nutrients. The glycocalyces found in a person's body are products of that person's genetic makeup. They give each of the individual's trillions of cells the "identity" of belonging in the person's body. This identity is the primary way that a person's immune defense cells "know" not to attack the person's own body cells, but it also is the reason organs donated by another person might be rejected.

Peripheral proteins are typically found on the inner or outer surface of the lipid bilayer but can also be attached to the internal or external surface of an integral protein. These proteins typically perform a specific function for the cell. Some peripheral proteins on the surface of intestinal cells, for example, act as digestive enzymes to break down nutrients to sizes that can pass through the cells and into the bloodstream.

Transport across the Cell Membrane

One of the great wonders of the cell membrane is its ability to regulate the concentration of substances inside the cell. These substances include ions such as Ca^{++}, Na^{+}, K^{+}, and Cl^{-}; nutrients including sugars, fatty acids, and amino acids; and waste products, particularly carbon dioxide (CO_2), which must leave the cell.

The membrane's lipid bilayer structure provides the first level of control. The phospholipids are tightly packed together, and the membrane has a hydrophobic interior. This structure causes the membrane to be selectively permeable. A membrane that has **selective permeability** allows only substances meeting certain criteria to pass through it unaided. In the case of the cell membrane, only relatively small, nonpolar materials can move through the lipid bilayer (remember, the lipid tails of the membrane are nonpolar). Some examples of these are other lipids, oxygen and carbon dioxide gases, and alcohol. However, water-soluble materials—like glucose, amino acids, and electrolytes—need some assistance to cross the membrane because they are repelled by the hydrophobic tails of the phospholipid bilayer. All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not energy is required. **Passive transport** is the movement of

diffuse down their concentration gradients, but because most substances cannot pass freely through the lipid bilayer of the cell membrane, their movement is restricted to protein channels and specialized transport mechanisms in the membrane. **Facilitated diffusion** is the diffusion process used for those substances that cannot cross the lipid bilayer due to their size, charge, and/or polarity (Figure 3.6). A common example of facilitated diffusion is the movement of glucose into the cell, where it is used to make ATP. Although glucose can be more concentrated outside of a cell, it cannot cross the lipid bilayer via simple diffusion because it is both large and polar. To resolve this, a specialized carrier protein called the glucose transporter will transfer glucose molecules into the cell to facilitate its inward diffusion.

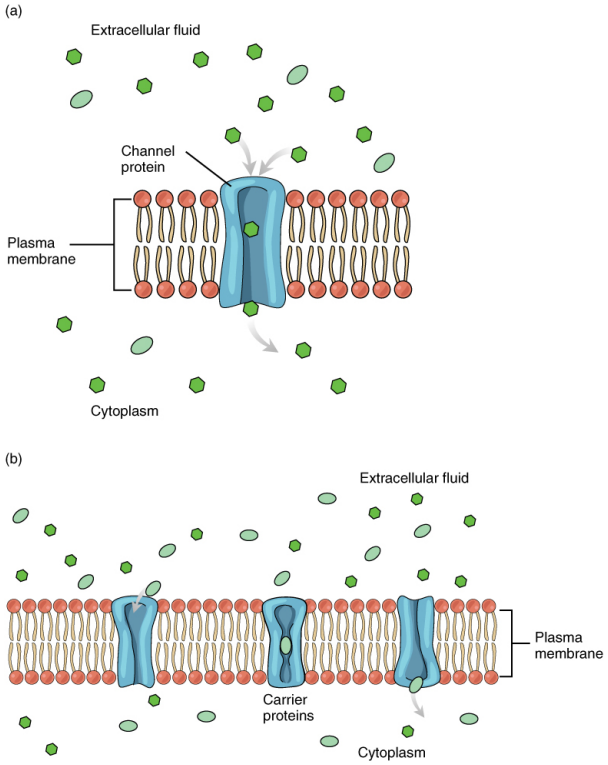


FIGURE 3.6 Facilitated Diffusion (a) Facilitated diffusion of substances crossing the cell (plasma) membrane takes place with the help of proteins such as channel proteins and carrier proteins. Channel proteins are less selective than carrier proteins, and usually mildly discriminate between their cargo based on size and charge. (b) Carrier proteins are more selective, often only allowing one particular type of molecule to cross.

As an example, even though sodium ions (Na^+) are highly concentrated outside of cells, these electrolytes are charged and cannot pass through the nonpolar lipid bilayer of the membrane. Their diffusion is facilitated by membrane proteins that form sodium channels (or "pores"), so that Na^+ ions can move down their concentration gradient from outside the cells to inside the cells. There are many other solutes that must undergo facilitated diffusion to move into a cell, such as amino acids, or to move out of a cell, such as wastes. Because facilitated diffusion is a passive process, it does not require energy expenditure by the cell.

Water also can move freely across the cell membrane of all cells, either through protein channels or by slipping between the lipid tails of the membrane itself. **Osmosis** is the diffusion of water through a semipermeable membrane (Figure 3.7).

ATP is required for these membrane proteins to transport substances—molecules or ions—across the membrane, usually against their concentration gradients (from an area of low concentration to an area of high concentration).

The **sodium-potassium pump**, which is also called Na^+/K^+ ATPase, transports sodium out of a cell while moving potassium into the cell. The Na^+/K^+ pump is an important ion pump found in the membranes of many types of cells. These pumps are particularly abundant in nerve cells, which are constantly pumping out sodium ions and pulling in potassium ions to maintain an electrical gradient across their cell membranes. An **electrical gradient** is a difference in electrical charge across a space. In the case of nerve cells, for example, the electrical gradient exists between the inside and outside of the cell, with the inside being negatively-charged (at around -70 mV) relative to the outside. The negative electrical gradient is maintained because each Na^+/K^+ pump moves three Na^+ ions out of the cell and two K^+ ions into the cell for each ATP molecule that is used (Figure 3.9). This process is so important for nerve cells that it accounts for the majority of their ATP usage.

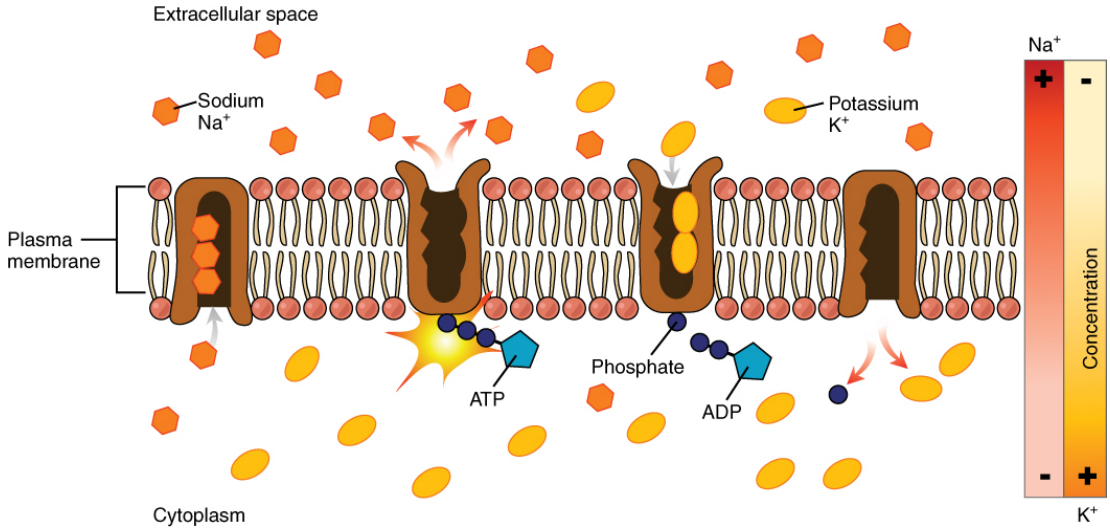


FIGURE 3.9 Sodium-Potassium Pump The sodium-potassium pump is found in many cell (plasma) membranes. Powered by ATP, the pump moves sodium and potassium ions in opposite directions, each against its concentration gradient. In a single cycle of the pump, three sodium ions are extruded from and two potassium ions are imported into the cell.

Active transport pumps can also work together with other active or passive transport systems to move substances across the membrane. For example, the sodium-potassium pump maintains a high concentration of sodium ions outside of the cell. Therefore, if the cell needs sodium ions, all it has to do is open a passive sodium channel, as the concentration gradient of the sodium ions will drive them to diffuse into the cell. In this way, the action of an active transport pump (the sodium-potassium pump) powers the passive transport of sodium ions by creating a concentration gradient. When active transport powers the transport of another substance in this way, it is called secondary active transport.

Symporters are secondary active transporters that move two substances in the same direction. For example, the sodium-glucose symporter uses sodium ions to “pull” glucose molecules into the cell. Because cells store glucose for energy, glucose is typically at a higher concentration inside of the cell than outside. However, due to the action of the sodium-potassium pump, sodium ions will easily diffuse into the cell when the symporter is opened. The flood of sodium ions through the symporter provides the energy that allows glucose to move through the symporter and into the cell, against its concentration gradient.

Conversely, antiporters are secondary active transport systems that transport substances in opposite directions. For example, the sodium-hydrogen ion antiporter uses the energy from the inward flood of sodium ions to move hydrogen ions (H+) out of the cell. The sodium-hydrogen antiporter is used to maintain the pH of the cell's interior.

Other forms of active transport do not involve membrane carriers. **Endocytosis** (bringing “into the cell”) is the process of a cell ingesting material by enveloping it in a portion of its cell membrane, and then pinching off that portion of membrane (Figure 3.10). Once pinched off, the portion of membrane and its contents becomes an independent, intracellular vesicle. A **vesicle** is a membranous sac—a spherical and hollow organelle bounded by a lipid bilayer membrane. Endocytosis often brings materials into the cell that must be broken down or digested.

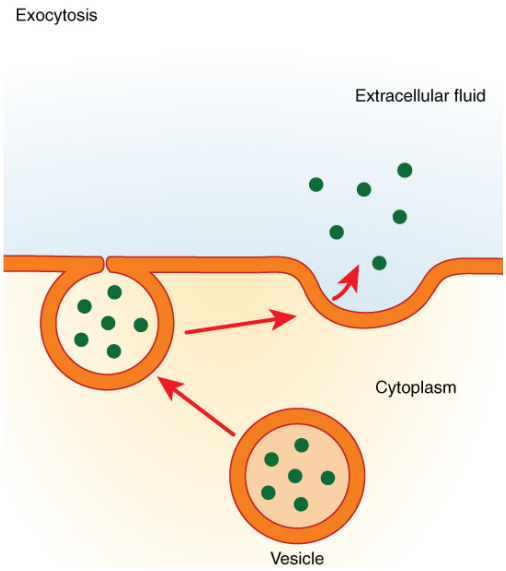


FIGURE 3.11 Exocytosis Exocytosis is much like endocytosis in reverse. Material destined for export is packaged into a vesicle inside the cell. The membrane of the vesicle fuses with the cell membrane, and the contents are released into the extracellular space.

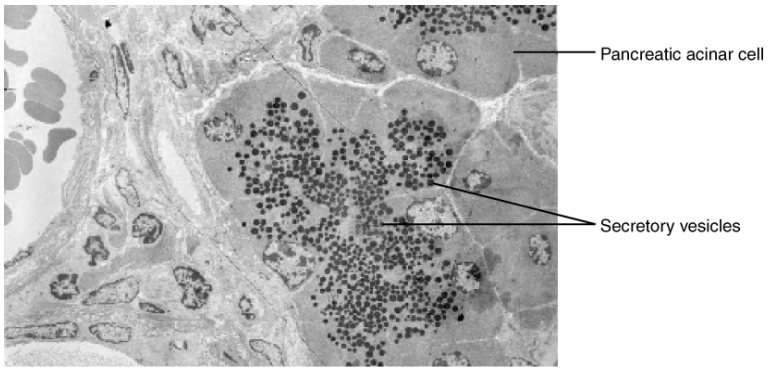


FIGURE 3.12 Pancreatic Cells' Enzyme Products The pancreatic acinar cells produce and secrete many enzymes that digest food. The tiny black granules in this electron micrograph are secretory vesicles filled with enzymes that will be exported from the cells via exocytosis. LM × 2900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/pcells) to explore the tissue sample in greater detail.

Diseases of the...

Cell: Cystic Fibrosis Cystic fibrosis (CF) affects approximately 30,000 people in the United States, with about 1,000 new cases reported each year. The genetic disease is most well known for its damage to the lungs, causing breathing difficulties and chronic lung infections, but it also affects the liver, pancreas, and intestines. Only about 50 years ago, the prognosis for children born with CF was very grim—a life expectancy rarely over 10 years. Today, with advances in medical treatment, many CF patients live into their 30s.

The symptoms of CF result from a malfunctioning membrane ion channel called the cystic fibrosis transmembrane conductance regulator, or CFTR. In healthy people, the CFTR protein is an integral membrane protein that transports Cl^- ions out of the cell. In a person who has CF, the gene for the CFTR is mutated, thus, the cell manufactures a defective channel protein that typically is not incorporated into the membrane, but is instead degraded by the cell.

The CFTR requires ATP in order to function, making its Cl^- transport a form of active transport. This characteristic puzzled researchers for a long time because the Cl^- ions are actually flowing *down* their

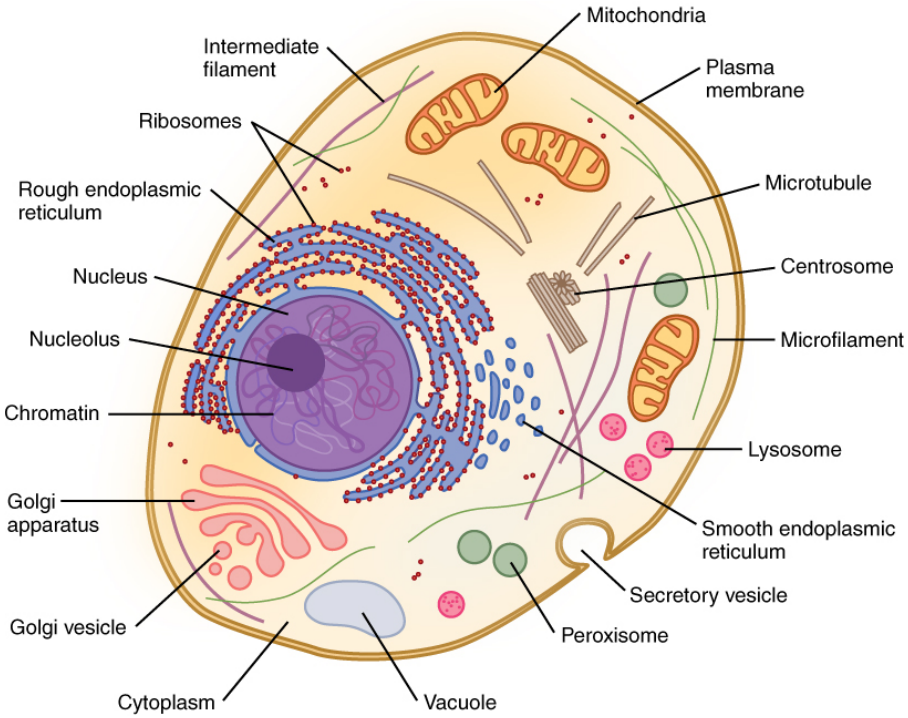


FIGURE 3.13 Prototypical Human Cell While this image is not indicative of any one particular human cell, it is a prototypical example of a cell containing the primary organelles and internal structures.

Organelles of the Endomembrane System

A set of three major organelles together form a system within the cell called the endomembrane system. These organelles work together to perform various cellular jobs, including the task of producing, packaging, and exporting certain cellular products. The organelles of the endomembrane system include the endoplasmic reticulum, Golgi apparatus, and vesicles.

Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is a system of channels that is continuous with the nuclear membrane (or "envelope") covering the nucleus and composed of the same lipid bilayer material. The ER can be thought of as a series of winding thoroughfares similar to the waterway canals in Venice. The ER provides passages throughout much of the cell that function in transporting, synthesizing, and storing materials. The winding structure of the ER results in a large membranous surface area that supports its many functions (Figure 3.14).

ER, much like a post-office. The Golgi apparatus looks like stacked flattened discs, almost like stacks of oddly shaped pancakes. Like the ER, these discs are membranous. The Golgi apparatus has two distinct sides, each with a different role. One side of the apparatus receives products in vesicles. These products are sorted through the apparatus, and then they are released from the opposite side after being repackaged into new vesicles. If the product is to be exported from the cell, the vesicle migrates to the cell surface and fuses to the cell membrane, and the cargo is secreted (Figure 3.15).

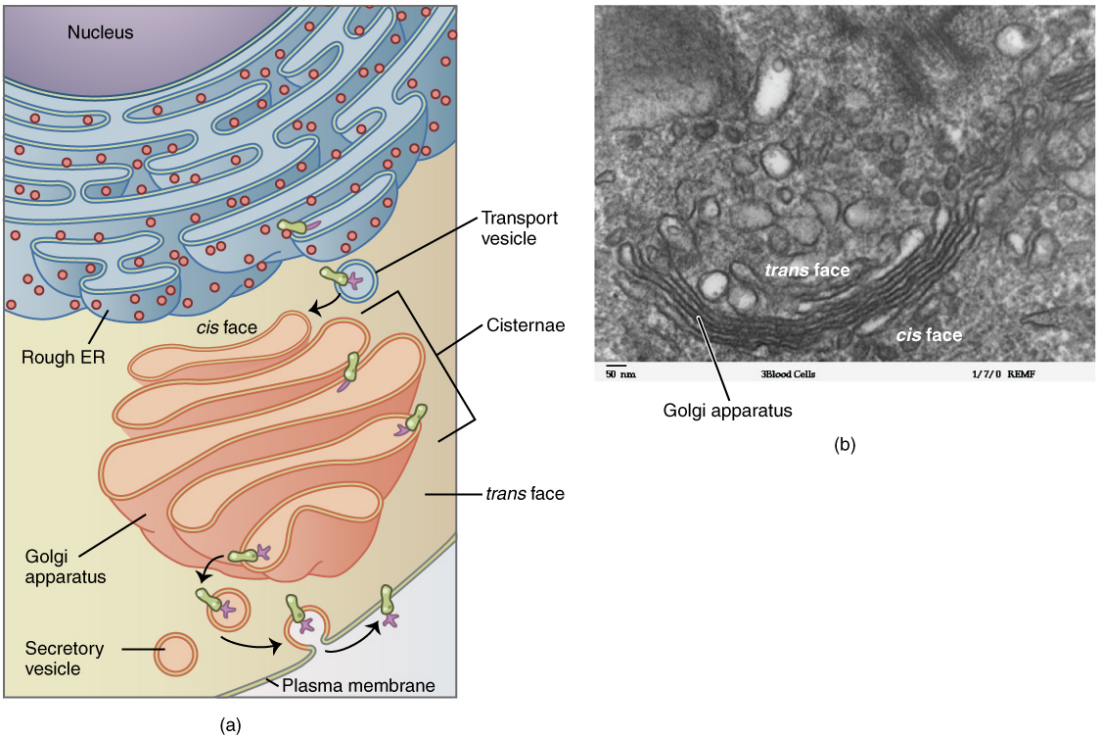


FIGURE 3.15 Golgi Apparatus (a) The Golgi apparatus manipulates products from the rough ER, and also produces new organelles called lysosomes. Proteins and other products of the ER are sent to the Golgi apparatus, which organizes, modifies, packages, and tags them. Some of these products are transported to other areas of the cell and some are exported from the cell through exocytosis. Enzymatic proteins are packaged as new lysosomes (or packaged and sent for fusion with existing lysosomes). (b) An electron micrograph of the Golgi apparatus.

Lysosomes

Some of the protein products packaged by the Golgi include digestive enzymes that are meant to remain inside the cell for use in breaking down certain materials. The enzyme-containing vesicles released by the Golgi may form new lysosomes, or fuse with existing, lysosomes. A **lysosome** is an organelle that contains enzymes that break down and digest unneeded cellular components, such as a damaged organelle. (A lysosome is similar to a wrecking crew that takes down old and unsound buildings in a neighborhood.) **Autophagy** ("self-eating") is the process of a cell digesting its own structures. Lysosomes are also important for breaking down foreign material. For example, when certain immune defense cells (white blood cells) phagocytize bacteria, the bacterial cell is transported into a lysosome and digested by the enzymes inside. As one might imagine, such phagocytic defense cells contain large numbers of lysosomes.

Under certain circumstances, lysosomes perform a more grand and dire function. In the case of damaged or unhealthy cells, lysosomes can be triggered to open up and release their digestive enzymes into the cytoplasm of the cell, killing the cell. This "self-destruct" mechanism is called **autolysis**, and makes the process of cell death controlled (a mechanism called "apoptosis").

INTERACTIVE LINK

Watch this video (http://openstax.org/l/endomembrane1) to learn about the endomembrane system, which includes the rough and smooth ER and the Golgi body as well as lysosomes and vesicles. What is the primary role of the endomembrane system?

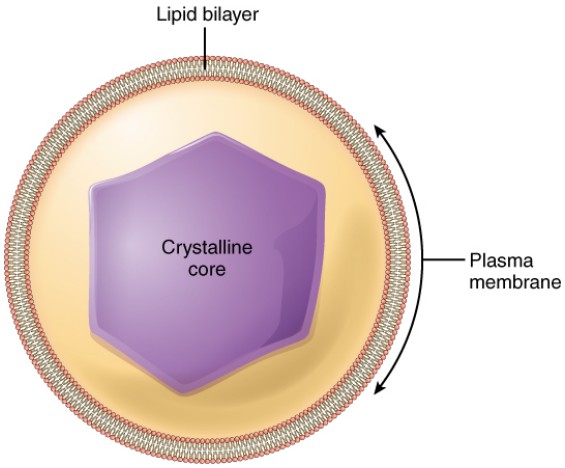


FIGURE 3.17 **Peroxisome** Peroxisomes are membrane-bound organelles that contain an abundance of enzymes for detoxifying harmful substances and lipid metabolism.

Reactive oxygen species (ROS) such as peroxides and free radicals are the highly reactive products of many normal cellular processes, including the mitochondrial reactions that produce ATP and oxygen metabolism. Examples of ROS include the hydroxyl radical OH, H_2O_2, and superoxide (O_2^-). Some ROS are important for certain cellular functions, such as cell signaling processes and immune responses against foreign substances. Free radicals are reactive because they contain free unpaired electrons; they can easily oxidize other molecules throughout the cell, causing cellular damage and even cell death. Free radicals are thought to play a role in many destructive processes in the body, from cancer to coronary artery disease.

Peroxisomes, on the other hand, oversee reactions that neutralize free radicals. Peroxisomes produce large amounts of the toxic H_2O_2 in the process, but peroxisomes contain enzymes that convert H_2O_2 into water and oxygen. These byproducts are safely released into the cytoplasm. Like miniature sewage treatment plants, peroxisomes neutralize harmful toxins so that they do not wreak havoc in the cells. The liver is the organ primarily responsible for detoxifying the blood before it travels throughout the body, and liver cells contain an exceptionally high number of peroxisomes.

Defense mechanisms such as detoxification within the peroxisome and certain cellular antioxidants serve to neutralize many of these molecules. Some vitamins and other substances, found primarily in fruits and vegetables, have antioxidant properties. Antioxidants work by being oxidized themselves, halting the destructive reaction cascades initiated by the free radicals. Sometimes though, ROS accumulate beyond the capacity of such defenses.

Oxidative stress is the term used to describe damage to cellular components caused by ROS. Due to their characteristic unpaired electrons, ROS can set off chain reactions where they remove electrons from other molecules, which then become oxidized and reactive, and do the same to other molecules, causing a chain reaction. ROS can cause permanent damage to cellular lipids, proteins, carbohydrates, and nucleic acids. Damaged DNA can lead to genetic mutations and even cancer. A **mutation** is a change in the nucleotide sequence in a gene within a cell's DNA, potentially altering the protein coded by that gene. Other diseases believed to be triggered or exacerbated by ROS include Alzheimer's disease, cardiovascular diseases, diabetes, Parkinson's disease, arthritis, Huntington's disease, and schizophrenia, among many others. It is noteworthy that these diseases are largely age-related. Many scientists believe that oxidative stress is a major contributor to the aging process.

Aging and the...

Cell: The Free Radical Theory

The free radical theory on aging was originally proposed in the 1950s, and still remains under debate. Generally speaking, the free radical theory of aging suggests that accumulated cellular damage from oxidative stress contributes to the physiological and anatomical effects of aging. There are two significantly different versions of this theory: one states that the aging process itself is a result of oxidative damage, and the other states that oxidative damage causes age-related disease and disorders. The latter version of the theory is more widely

a protein that forms chains, is the primary component of these microfilaments. Actin fibers, twisted chains of actin filaments, constitute a large component of muscle tissue and, along with the protein myosin, are responsible for muscle contraction. Like microtubules, actin filaments are long chains of single subunits (called actin subunits). In muscle cells, these long actin strands, called thin filaments, are "pulled" by thick filaments of the myosin protein to contract the cell.

Actin also has an important role during cell division. When a cell is about to split in half during cell division, actin filaments work with myosin to create a cleavage furrow that eventually splits the cell down the middle, forming two new cells from the original cell.

The final cytoskeletal filament is the intermediate filament. As its name would suggest, an **intermediate filament** is a filament intermediate in thickness between the microtubules and microfilaments (see Figure 3.18**c**). Intermediate filaments are made up of long fibrous subunits of a protein called keratin that are wound together like the threads that compose a rope. Intermediate filaments, in concert with the microtubules, are important for maintaining cell shape and structure. Unlike the microtubules, which resist compression, intermediate filaments resist tension—the forces that pull apart cells. There are many cases in which cells are prone to tension, such as when epithelial cells of the skin are compressed, tugging them in different directions. Intermediate filaments help anchor organelles together within a cell and also link cells to other cells by forming special cell-to-cell junctions.

3.3 The Nucleus and DNA Replication

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure and features of the nuclear membrane
- List the contents of the nucleus
- Explain the organization of the DNA molecule within the nucleus
- Describe the process of DNA replication

The nucleus is the largest and most prominent of a cell's organelles (Figure 3.19). The nucleus is generally considered the control center of the cell because it stores all of the genetic instructions for manufacturing proteins. Interestingly, some cells in the body, such as muscle cells, contain more than one nucleus (Figure 3.20), which is known as multinucleated. Other cells, such as mammalian red blood cells (RBCs), do not contain nuclei at all. RBCs eject their nuclei as they mature, making space for the large numbers of hemoglobin molecules that carry oxygen throughout the body (Figure 3.21). Without nuclei, the life span of RBCs is short, and so the body must produce new ones constantly.

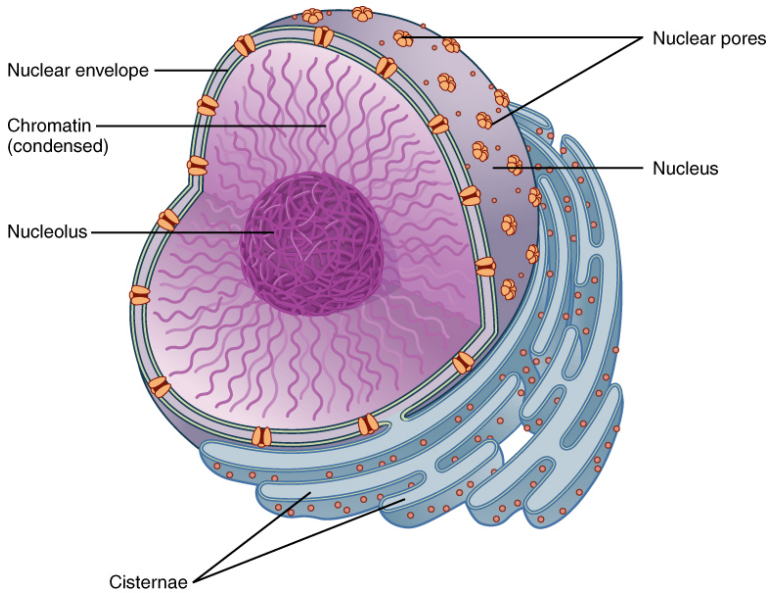


FIGURE 3.19 The Nucleus The nucleus is the control center of the cell. The nucleus of living cells contains the genetic material that determines the entire structure and function of that cell.

the passage of materials into and out of the nucleus.

Inside the nuclear envelope is a gel-like nucleoplasm with solutes that include the building blocks of nucleic acids. There also can be a dark-staining mass often visible under a simple light microscope, called a **nucleolus** (plural = nucleoli). The nucleolus is a region of the nucleus that is responsible for manufacturing the RNA necessary for construction of ribosomes. Once synthesized, newly made ribosomal subunits exit the cell's nucleus through the nuclear pores.

The genetic instructions that are used to build and maintain an organism are arranged in an orderly manner in strands of DNA. Within the nucleus are threads of **chromatin** composed of DNA and associated proteins (Figure 3.22). Along the chromatin threads, the DNA is wrapped around a set of **histone** proteins. A **nucleosome** is a single, wrapped DNA-histone complex. Multiple nucleosomes along the entire molecule of DNA appear like a beaded necklace, in which the string is the DNA and the beads are the associated histones. When a cell is in the process of division, the chromatin condenses into chromosomes, so that the DNA can be safely transported to the "daughter cells." The **chromosome** is composed of DNA and proteins; it is the condensed form of chromatin. It is estimated that humans have almost 22,000 genes distributed on 46 chromosomes.

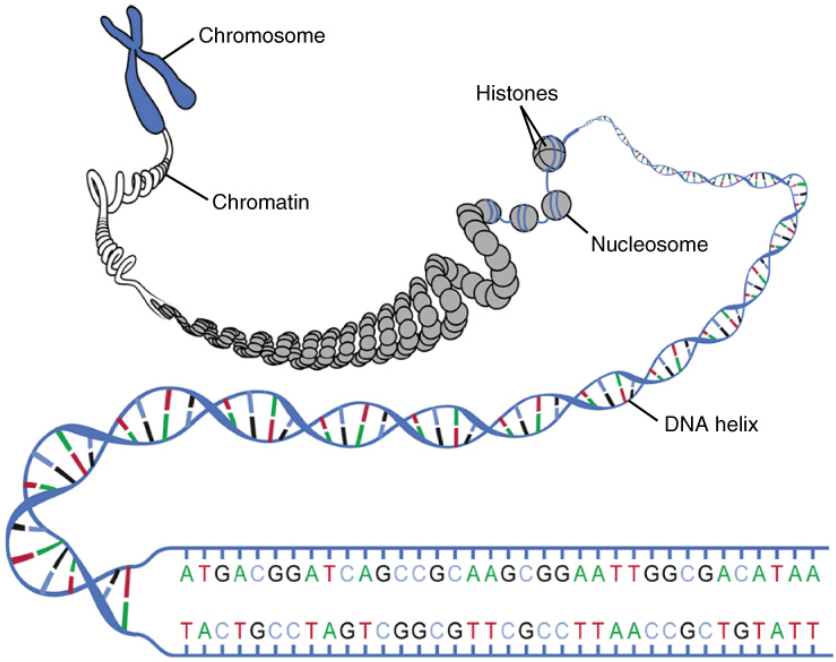


FIGURE 3.22 DNA Macrostructure Strands of DNA are wrapped around supporting histones. These proteins are increasingly bundled and condensed into chromatin, which is packed tightly into chromosomes when the cell is ready to divide.

DNA Replication

In order for an organism to grow, develop, and maintain its health, cells must reproduce themselves by dividing to produce two new daughter cells, each with the full complement of DNA as found in the original cell. Billions of new cells are produced in an adult human every day. Only very few cell types in the body do not divide, including nerve cells, skeletal muscle fibers, and cardiac muscle cells. The division time of different cell types varies. Epithelial cells of the skin and gastrointestinal lining, for instance, divide very frequently to replace those that are constantly being rubbed off of the surface by friction.

A DNA molecule is made of two strands that "complement" each other in the sense that the molecules that compose the strands fit together and bind to each other, creating a double-stranded molecule that looks much like a long, twisted ladder. This double helix can be constructed easily because the two strands are antiparallel, meaning the two strands run in opposite directions. Each side rail of the DNA ladder is composed of alternating sugar and phosphate groups (Figure 3.23). The two sides of the ladder are not identical, but are complementary. These two backbones are bonded to each other across pairs of protruding bases, each bonded pair forming one "rung," or cross member. The four DNA bases are adenine (A), thymine (T), cytosine (C), and guanine (G). Because of their shape and charge, the two bases that compose a pair always bond together. Adenine always binds with thymine, and

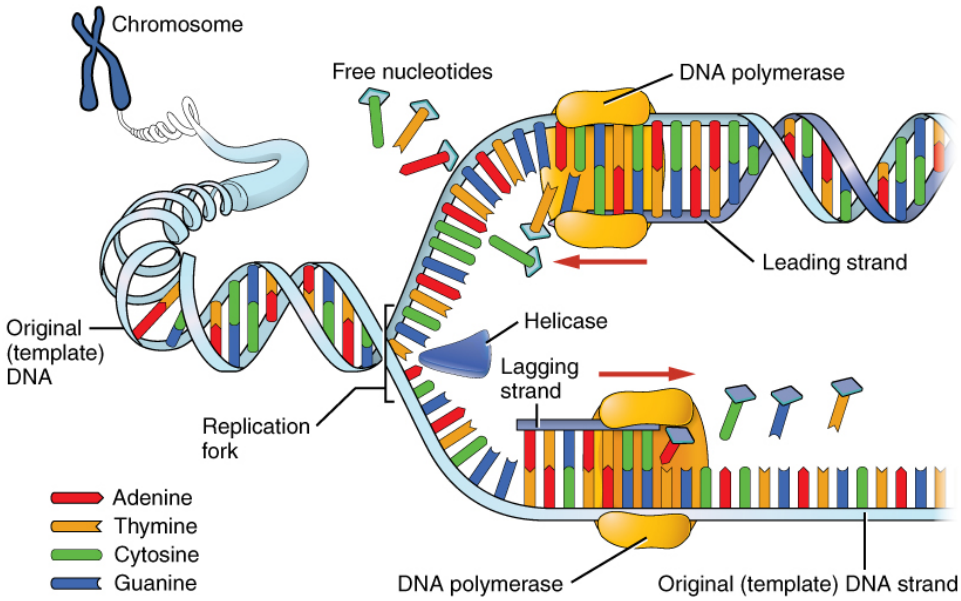


FIGURE 3.24 DNA Replication DNA replication faithfully duplicates the entire genome of the cell. During DNA replication, a number of different enzymes work together to pull apart the two strands so each strand can be used as a template to synthesize new complementary strands. The two new daughter DNA molecules each contain one pre-existing strand and one newly synthesized strand. Thus, DNA replication is said to be "semiconservative."

Stage 1: Initiation. The two complementary strands are separated, much like unzipping a zipper. Special enzymes, including **helicase**, untwist and separate the two strands of DNA.

Stage 2: Elongation. Each strand becomes a template along which a new complementary strand is built. **DNA polymerase** brings in the correct bases to complement the template strand, synthesizing a new strand base by base. A DNA polymerase is an enzyme that adds free nucleotides to the end of a chain of DNA, making a new double strand. This growing strand continues to be built until it has fully complemented the template strand.

Stage 3: Termination. Once the two original strands are bound to their own, finished, complementary strands, DNA replication is stopped and the two new identical DNA molecules are complete.

Each new DNA molecule contains one strand from the original molecule and one newly synthesized strand. The term for this mode of replication is "semiconservative," because half of the original DNA molecule is conserved in each new DNA molecule. This process continues until the cell's entire **genome**, the entire complement of an organism's DNA, is replicated. As you might imagine, it is very important that DNA replication take place precisely so that new cells in the body contain the exact same genetic material as their parent cells. Mistakes made during DNA replication, such as the accidental addition of an inappropriate nucleotide, have the potential to render a gene dysfunctional or useless. Fortunately, there are mechanisms in place to minimize such mistakes. A DNA proofreading process enlists the help of special enzymes that scan the newly synthesized molecule for mistakes and corrects them. Once the process of DNA replication is complete, the cell is ready to divide. You will explore the process of cell division later in the chapter.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/DNArep) to learn about DNA replication. DNA replication proceeds simultaneously at several sites on the same molecule. What separates the base pair at the start of DNA replication?

atom compared with DNA. Finally, instead of the base thymine, RNA contains the base uracil. This means that adenine will always pair up with uracil during the protein synthesis process.

Gene expression begins with the process called **transcription**, which is the synthesis of a strand of mRNA that is complementary to the gene of interest. This process is called transcription because the mRNA is like a transcript, or copy, of the gene's DNA code. Transcription begins in a fashion somewhat like DNA replication, in that a region of DNA unwinds and the two strands separate, however, only that small portion of the DNA will be split apart. The triplets within the gene on this section of the DNA molecule are used as the template to transcribe the complementary strand of RNA (Figure 3.26). A **codon** is a three-base sequence of mRNA, so-called because they directly encode amino acids. Like DNA replication, there are three stages to transcription: initiation, elongation, and termination.

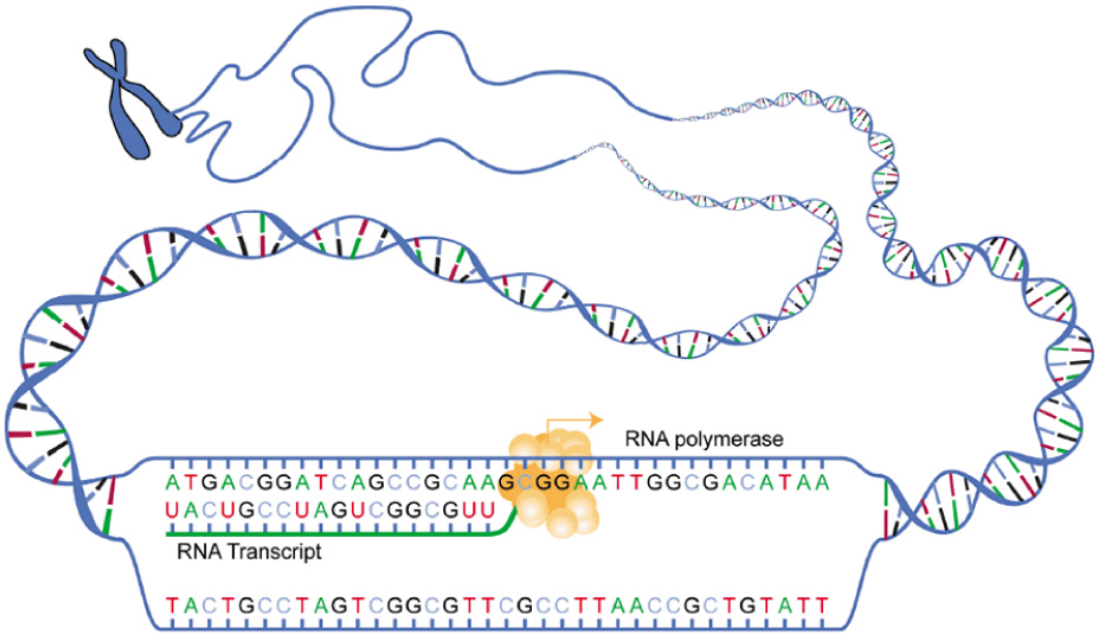


FIGURE 3.26 Transcription: from DNA to mRNA In the first of the two stages of making protein from DNA, a gene on the DNA molecule is transcribed into a complementary mRNA molecule.

Stage 1: Initiation. A region at the beginning of the gene called a **promoter**—a particular sequence of nucleotides—triggers the start of transcription.

Stage 2: Elongation. Transcription starts when RNA polymerase unwinds the DNA segment. One strand, referred to as the coding strand, becomes the template with the genes to be coded. The polymerase then aligns the correct nucleic acid (A, C, G, or U) with its complementary base on the coding strand of DNA. **RNA polymerase** is an enzyme that adds new nucleotides to a growing strand of RNA. This process builds a strand of mRNA.

Stage 3: Termination. At the end of the gene, a sequence of nucleotides called the terminator sequence causes the new RNA to fold up on itself. This fold causes the RNA to separate from the gene and from RNA polymerase, ending transcription.

Before the mRNA molecule leaves the nucleus and proceeds to protein synthesis, it is modified in a number of ways. For this reason, it is often called a pre-mRNA at this stage. For example, your DNA, and thus complementary mRNA, contains long regions called non-coding regions that do not code for amino acids. Their function is still a mystery, but the process called **splicing** removes these non-coding regions from the pre-mRNA transcript (Figure 3.27). A **spliceosome**—a structure composed of various proteins and other molecules—attaches to the mRNA and "splices" or cuts out the non-coding regions. The removed segment of the transcript is called an **intron**. The remaining exons are pasted together. An **exon** is a segment of RNA that remains after splicing. Interestingly, some introns that are removed from mRNA are not always non-coding. When different coding regions of mRNA are spliced out, different variations of the protein will eventually result, with differences in structure and function. This process results in a much larger variety of possible proteins and protein functions. When the mRNA transcript is ready, it travels out of the nucleus and into the cytoplasm.

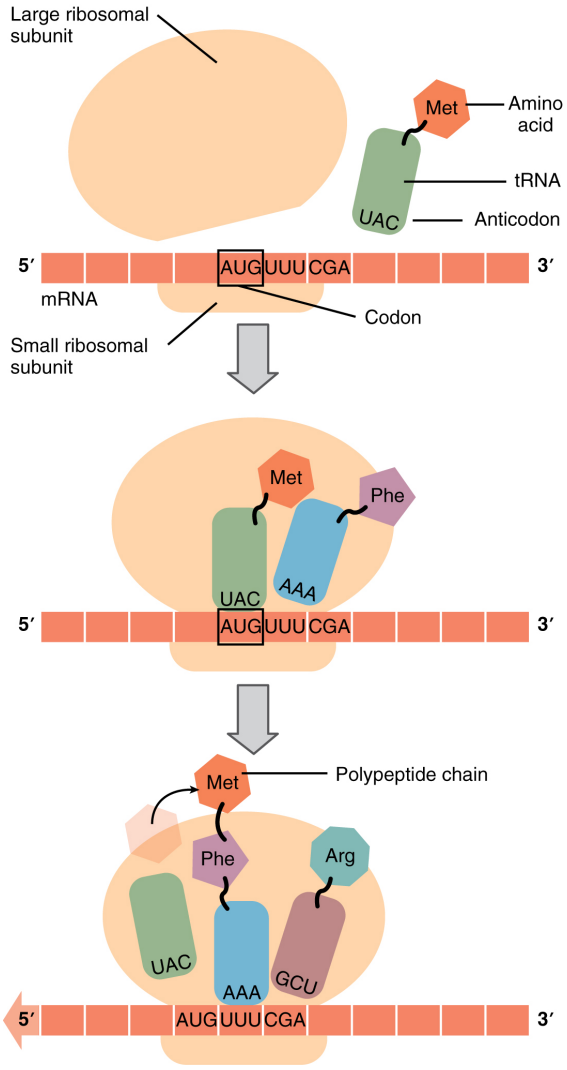


FIGURE 3.28 Translation from RNA to Protein During translation, the mRNA transcript is "read" by a functional complex consisting of the ribosome and tRNA molecules. tRNAs bring the appropriate amino acids in sequence to the growing polypeptide chain by matching their anti-codons with codons on the mRNA strand.

Much like the processes of DNA replication and transcription, translation consists of three main stages: initiation, elongation, and termination. Initiation takes place with the binding of a ribosome to an mRNA transcript. The elongation stage involves the recognition of a tRNA anticodon with the next mRNA codon in the sequence. Once the anticodon and codon sequences are bound (remember, they are complementary base pairs), the tRNA presents its amino acid cargo and the growing polypeptide strand is attached to this next amino acid. This attachment takes place with the assistance of various enzymes and requires energy. The tRNA molecule then releases the mRNA strand, the mRNA strand shifts one codon over in the ribosome, and the next appropriate tRNA arrives with its matching anticodon. This process continues until the final codon on the mRNA is reached which provides a "stop" message that signals termination of translation and triggers the release of the complete, newly synthesized protein. Thus, a gene within the DNA molecule is transcribed into mRNA, which is then translated into a protein product (Figure 3.29).

The Cell Cycle

One "turn" or cycle of the cell cycle consists of two general phases: interphase, followed by mitosis and cytokinesis. **Interphase** is the period of the cell cycle during which the cell is not dividing. The majority of cells are in interphase most of the time. **Mitosis** is the division of genetic material, during which the cell nucleus breaks down and two new, fully functional, nuclei are formed. **Cytokinesis** divides the cytoplasm into two distinctive cells.

Interphase

A cell grows and carries out all normal metabolic functions and processes in a period called G_1 (Figure 3.30). **G_1 phase** (gap 1 phase) is the first gap, or growth phase in the cell cycle. For cells that will divide again, G_1 is followed by replication of the DNA, during the S phase. The **S phase** (synthesis phase) is period during which a cell replicates its DNA.

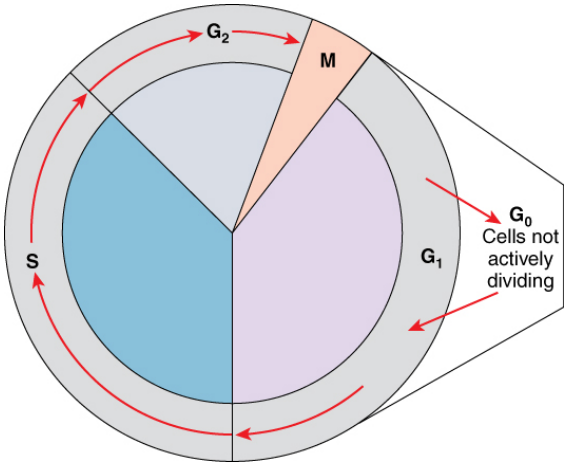


FIGURE 3.30 Cell Cycle The two major phases of the cell cycle include mitosis (designated M), when the cell divides, and interphase, when the cell grows and performs all of its normal functions. Interphase is further subdivided into G_1, S, and G_2 phases.

After the synthesis phase, the cell proceeds through the G_2 phase. The **G_2 phase** is a second gap phase, during which the cell continues to grow and makes the necessary preparations for mitosis. Between G_1, S, and G_2 phases, cells will vary the most in their duration of the G1 phase. It is here that a cell might spend a couple of hours, or many days. The S phase typically lasts between 8-10 hours and the G_2 phase approximately 5 hours. In contrast to these phases, the **G_0 phase** is a resting phase of the cell cycle. Cells that have temporarily stopped dividing and are resting (a common condition) and cells that have permanently ceased dividing (like nerve cells) are said to be in G_0.

The Structure of Chromosomes

Billions of cells in the human body divide every day. During the synthesis phase (S, for DNA synthesis) of interphase, the amount of DNA within the cell precisely doubles. Therefore, after DNA replication but before cell division, each cell actually contains *two* copies of each chromosome. Each copy of the chromosome is referred to as a **sister chromatid** and is physically bound to the other copy.(Note that the term "sister chromatid" is used regardless of the sex of the person.) The **centromere** is the structure that attaches one sister chromatid to another. Because a human cell has 46 chromosomes, during this phase, there are 92 chromatids (46 × 2) in the cell. Make sure not to confuse the concept of a pair of chromatids (one chromosome and its exact copy attached during mitosis) and a homologous pair of chromosomes (two paired chromosomes which were inherited separately, one from each parent) (Figure 3.31).

Prophase is the first phase of mitosis, during which the loosely packed chromatin coils and condenses into visible chromosomes. During prophase, each chromosome becomes visible with its identical partner attached, forming the familiar X-shape of sister chromatids. The nucleolus disappears early during this phase, and the nuclear envelope also disintegrates.

A major occurrence during prophase concerns a very important structure that contains the origin site for microtubule growth. Recall the cellular structures called centrioles that serve as origin points from which microtubules extend. These tiny structures also play a very important role during mitosis. A **centrosome** is a pair of centrioles together. The cell contains two centrosomes side-by-side, which begin to move apart during prophase. As the centrosomes migrate to two different sides of the cell, microtubules begin to extend from each like long fingers from two hands extending toward each other. The **mitotic spindle** is the structure composed of the centrosomes and their emerging microtubules.

Near the end of prophase there is an invasion of the nuclear area by microtubules from the mitotic spindle. The nuclear membrane has disintegrated, and the microtubules attach themselves to the centromeres that adjoin pairs of sister chromatids. The **kinetochore** is a protein structure on the centromere that is the point of attachment between the mitotic spindle and the sister chromatids. This stage is referred to as late prophase or "prometaphase" to indicate the transition between prophase and metaphase.

Metaphase is the second stage of mitosis. During this stage, the sister chromatids, with their attached microtubules, line up along a linear plane in the middle of the cell. A metaphase plate forms between the centrosomes that are now located at either end of the cell. The **metaphase plate** is the name for the plane through the center of the spindle on which the sister chromatids are positioned. The microtubules are now poised to pull apart the sister chromatids and bring one from each pair to each side of the cell.

Anaphase is the third stage of mitosis. Anaphase takes place over a few minutes, when the pairs of sister chromatids are separated from one another, forming individual chromosomes once again. These chromosomes are pulled to opposite ends of the cell by their kinetochores, as the microtubules shorten. Each end of the cell receives one partner from each pair of sister chromatids, ensuring that the two new daughter cells will contain identical genetic material.

Telophase is the final stage of mitosis. Telophase is characterized by the formation of two new daughter nuclei at either end of the dividing cell. These newly formed nuclei surround the genetic material, which uncoils such that the chromosomes return to loosely packed chromatin. Nucleoli also reappear within the new nuclei, and the mitotic spindle breaks apart, each new cell receiving its own complement of DNA, organelles, membranes, and centrioles. At this point, the cell is already beginning to split in half as cytokinesis begins.

The **cleavage furrow** is a contractile band made up of microfilaments that forms around the midline of the cell during cytokinesis. (Recall that microfilaments consist of actin.) This contractile band squeezes the two cells apart until they finally separate. Two new cells are now formed. One of these cells (the "stem cell") enters its own cell cycle; able to grow and divide again at some future time. The other cell transforms into the functional cell of the tissue, typically replacing an "old" cell there.

Imagine a cell that completed mitosis but never underwent cytokinesis. In some cases, a cell may divide its genetic material and grow in size, but fail to undergo cytokinesis. This results in larger cells with more than one nucleus. Usually this is an unwanted aberration and can be a sign of cancerous cells.

Cell Cycle Control

A very elaborate and precise system of regulation controls direct the way cells proceed from one phase to the next in the cell cycle and begin mitosis. The control system involves molecules within the cell as well as external triggers. These internal and external control triggers provide "stop" and "advance" signals for the cell. Precise regulation of the cell cycle is critical for maintaining the health of an organism, and loss of cell cycle control can lead to cancer.

Mechanisms of Cell Cycle Control

As the cell proceeds through its cycle, each phase involves certain processes that must be completed before the cell should advance to the next phase. A **checkpoint** is a point in the cell cycle at which the cycle can be signaled to move forward or stopped. At each of these checkpoints, different varieties of molecules provide the stop or go

provide stop and go signals to regulate movement forward to the next phase. These signals are maintained in an intricate balance so that the cell only proceeds to the next phase when it is ready. This homeostatic control of the cell cycle can be thought of like a car's cruise control. Cruise control will continually apply just the right amount of acceleration to maintain a desired speed, unless the driver hits the brakes, in which case the car will slow down. Similarly, the cell includes molecular messengers, such as cyclins, that push the cell forward in its cycle.

In addition to cyclins, a class of proteins that are encoded by genes called proto-oncogenes provide important signals that regulate the cell cycle and move it forward. Examples of proto-oncogene products include cell-surface receptors for growth factors, or cell-signaling molecules, two classes of molecules that can promote DNA replication and cell division. In contrast, a second class of genes known as tumor suppressor genes sends stop signals during a cell cycle. For example, certain protein products of tumor suppressor genes signal potential problems with the DNA and thus stop the cell from dividing, while other proteins signal the cell to die if it is damaged beyond repair. Some tumor suppressor proteins also signal a sufficient surrounding cellular density, which indicates that the cell need not presently divide. The latter function is uniquely important in preventing tumor growth: normal cells exhibit a phenomenon called "contact inhibition;" thus, extensive cellular contact with neighboring cells causes a signal that stops further cell division.

These two contrasting classes of genes, proto-oncogenes and tumor suppressor genes, are like the accelerator and brake pedal of the cell's own "cruise control system," respectively. Under normal conditions, these stop and go signals are maintained in a homeostatic balance. Generally speaking, there are two ways that the cell's cruise control can lose control: a malfunctioning (overactive) accelerator, or a malfunctioning (underactive) brake. When compromised through a mutation, or otherwise altered, proto-oncogenes can be converted to oncogenes, which produce oncoproteins that push a cell forward in its cycle and stimulate cell division even when it is undesirable to do so. For example, a cell that should be programmed to self-destruct (a process called apoptosis) due to extensive DNA damage might instead be triggered to proliferate by an oncoprotein. On the other hand, a dysfunctional tumor suppressor gene may fail to provide the cell with a necessary stop signal, also resulting in unwanted cell division and proliferation.

A delicate homeostatic balance between the many proto-oncogenes and tumor suppressor genes delicately controls the cell cycle and ensures that only healthy cells replicate. Therefore, a disruption of this homeostatic balance can cause aberrant cell division and cancerous growths.

INTERACTIVE LINK

Visit this link (http://openstax.org/l/mitosis) to learn about mitosis. Mitosis results in two identical diploid cells. What structures forms during prophase?

3.6 Cellular Differentiation

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss how the generalized cells of a developing embryo or the stem cells of an adult organism become differentiated into specialized cells
- Distinguish between the categories of stem cells

How does a complex organism such as a human develop from a single cell—a fertilized egg—into the vast array of cell types such as nerve cells, muscle cells, and epithelial cells that characterize the adult? Throughout development and adulthood, the process of cellular differentiation leads cells to assume their final morphology and physiology. Differentiation is the process by which unspecialized cells become specialized to carry out distinct functions.

Stem Cells

A **stem cell** is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate.

blood cells.

Differentiation

When a cell differentiates (becomes more specialized), it may undertake major changes in its size, shape, metabolic activity, and overall function. Because all cells in the body, beginning with the fertilized egg, contain the same DNA, how do the different cell types come to be so different? The answer is analogous to a movie script. The different actors in a movie all read from the same script, however, they are each only reading their own part of the script. Similarly, all cells contain the same full complement of DNA, but each type of cell only "reads" the portions of DNA that are relevant to its own function. In biology, this is referred to as the unique genetic expression of each cell.

In order for a cell to differentiate into its specialized form and function, it need only manipulate those genes (and thus those proteins) that will be expressed, and not those that will remain silent. The primary mechanism by which genes are turned "on" or "off" is through transcription factors. A **transcription factor** is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription (Figure 3.35).

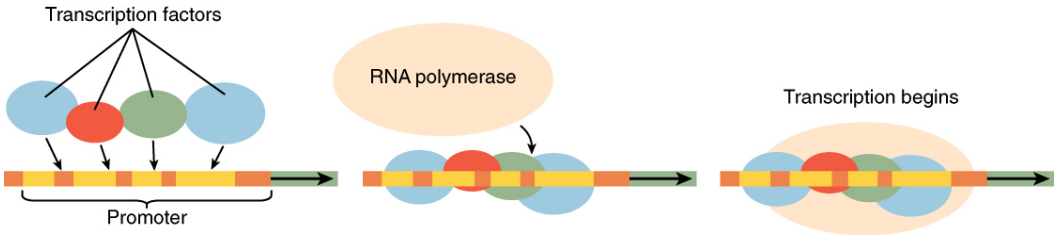


FIGURE 3.35 Transcription Factors Regulate Gene Expression While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors are proteins that affect the binding of RNA polymerase to a particular gene on the DNA molecule.

Everyday Connection

Stem Cell Research

Stem cell research aims to find ways to use stem cells to regenerate and repair cellular damage. Over time, most adult cells undergo the wear and tear of aging and lose their ability to divide and repair themselves. Stem cells do not display a particular morphology or function. Adult stem cells, which exist as a small subset of cells in most tissues, keep dividing and can differentiate into a number of specialized cells generally formed by that tissue. These cells enable the body to renew and repair body tissues.

The mechanisms that induce a non-differentiated cell to become a specialized cell are poorly understood. In a laboratory setting, it is possible to induce stem cells to differentiate into specialized cells by changing the physical and chemical conditions of growth. Several sources of stem cells are used experimentally and are classified according to their origin and potential for differentiation. Human embryonic stem cells (hESCs) are extracted from embryos and are pluripotent. The adult stem cells that are present in many organs and differentiated tissues, such as bone marrow and skin, are multipotent, being limited in differentiation to the types of cells found in those tissues. The stem cells isolated from umbilical cord blood are also multipotent, as are cells from deciduous teeth (baby teeth). Researchers have recently developed induced pluripotent stem cells (iPSCs) from mouse and human adult stem cells. These cells are genetically reprogrammed multipotent adult cells that function like embryonic stem cells; they are capable of generating cells characteristic of all three germ layers.

Because of their capacity to divide and differentiate into specialized cells, stem cells offer a potential treatment for diseases such as diabetes and heart disease (Figure 3.36). Cell-based therapy refers to treatment in which stem cells induced to differentiate in a growth dish are injected into a patient to repair damaged or destroyed cells or tissues. Many obstacles must be overcome for the application of cell-based therapy. Although embryonic stem cells have a nearly unlimited range of differentiation potential, they are seen as foreign by the patient's immune system and may trigger rejection. Also, the destruction of embryos to isolate embryonic stem cells raises considerable ethical and legal questions.

Key Terms

active transport form of transport across the cell membrane that requires input of cellular energy
amphipathic describes a molecule that exhibits a difference in polarity between its two ends, resulting in a difference in water solubility
anaphase third stage of mitosis (and meiosis), during which sister chromatids separate into two new nuclear regions of a dividing cell
anticodon consecutive sequence of three nucleotides on a tRNA molecule that is complementary to a specific codon on an mRNA molecule
autolysis breakdown of cells by their own enzymatic action
autophagy lysosomal breakdown of a cell's own components
cell cycle life cycle of a single cell, from its birth until its division into two new daughter cells
cell membrane membrane surrounding all animal cells, composed of a lipid bilayer interspersed with various molecules; also known as plasma membrane
centriole small, self-replicating organelle that provides the origin for microtubule growth and moves DNA during cell division
centromere region of attachment for two sister chromatids
centrosome cellular structure that organizes microtubules during cell division
channel protein membrane-spanning protein that has an inner pore which allows the passage of one or more substances
checkpoint progress point in the cell cycle during which certain conditions must be met in order for the cell to proceed to a subsequence phase
chromatin substance consisting of DNA and associated proteins
chromosome condensed version of chromatin
cilia small appendage on certain cells formed by microtubules and modified for movement of materials across the cellular surface
cleavage furrow contractile ring that forms around a cell during cytokinesis that pinches the cell into two halves
codon consecutive sequence of three nucleotides on an mRNA molecule that corresponds to a specific amino acid
concentration gradient difference in the concentration of a substance between two regions
cyclin one of a group of proteins that function in the progression of the cell cycle
cyclin-dependent kinase (CDK) one of a group of enzymes associated with cyclins that help them perform their functions
cytokinesis final stage in cell division, where the cytoplasm divides to form two separate daughter cells
cytoplasm internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials
cytoskeleton "skeleton" of a cell; formed by rod-like proteins that support the cell's shape and provide, among other functions, locomotive abilities
cytosol clear, semi-fluid medium of the cytoplasm, made up mostly of water
diffusion movement of a substance from an area of higher concentration to one of lower concentration
diploid condition marked by the presence of a double complement of genetic material (two sets of chromosomes, one set inherited from each of two parents)
DNA polymerase enzyme that functions in adding new nucleotides to a growing strand of DNA during DNA replication
DNA replication process of duplicating a molecule of DNA
electrical gradient difference in the electrical charge (potential) between two regions
endocytosis import of material into the cell by formation of a membrane-bound vesicle
endoplasmic reticulum (ER) cellular organelle that consists of interconnected membrane-bound tubules, which may or may not be associated with ribosomes (rough type or smooth type, respectively)
exocytosis export of a substance out of a cell by formation of a membrane-bound vesicle
exon one of the coding regions of an mRNA molecule that remain after splicing
extracellular fluid (ECF) fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluid found in other reservoirs in the body
facilitated diffusion diffusion of a substance with the aid of a membrane protein
flagellum appendage on certain cells formed by microtubules and modified for movement
G_0 phase phase of the cell cycle, usually entered from the G_1 phase; characterized by long or permanent periods where the cell does not move forward into the DNA synthesis phase
G_1 phase first phase of the cell cycle, after a new cell is born
G_2 phase third phase of the cell cycle, after the DNA synthesis phase

membrane that does not require input of cellular energy

peripheral protein membrane-associated protein that does not span the width of the lipid bilayer, but is attached peripherally to integral proteins, membrane lipids, or other components of the membrane

peroxisome membrane-bound organelle that contains enzymes primarily responsible for detoxifying harmful substances

phagocytosis endocytosis of large particles

pinocytosis endocytosis of fluid

pluripotent describes the condition of being able to differentiate into a large variety of cell types

polypeptide chain of amino acids linked by peptide bonds

polyribosome simultaneous translation of a single mRNA transcript by multiple ribosomes

promoter region of DNA that signals transcription to begin at that site within the gene

prophase first stage of mitosis (and meiosis), characterized by breakdown of the nuclear envelope and condensing of the chromatin to form chromosomes

proteome full complement of proteins produced by a cell (determined by the cell's specific gene expression)

reactive oxygen species (ROS) a group of extremely reactive peroxides and oxygen-containing radicals that may contribute to cellular damage

receptor protein molecule that contains a binding site for another specific molecule (called a ligand)

receptor-mediated endocytosis endocytosis of ligands attached to membrane-bound receptors

ribosomal RNA (rRNA) RNA that makes up the subunits of a ribosome

ribosome cellular organelle that functions in protein synthesis

RNA polymerase enzyme that unwinds DNA and then adds new nucleotides to a growing strand of RNA for the transcription phase of protein synthesis

S phase stage of the cell cycle during which DNA replication occurs

selective permeability feature of any barrier that allows certain substances to cross but excludes others

sister chromatid one of a pair of identical chromosomes, formed during DNA replication

sodium-potassium pump (also, Na^+/K^+ ATP-ase) membrane-embedded protein pump that uses ATP to move Na^+ out of a cell and K^+ into the cell

somatic cell all cells of the body excluding gamete cells

spliceosome complex of enzymes that serves to splice out the introns of a pre-mRNA transcript

splicing the process of modifying a pre-mRNA transcript by removing certain, typically non-coding, regions

stem cell cell that is oligo-, multi-, or pleuripotent that has the ability to produce additional stem cells rather than becoming further specialized

telophase final stage of mitosis (and meiosis), preceding cytokinesis, characterized by the formation of two new daughter nuclei

totipotent embryonic cells that have the ability to differentiate into any type of cell and organ in the body

transcription process of producing an mRNA molecule that is complementary to a particular gene of DNA

transcription factor one of the proteins that regulate the transcription of genes

transfer RNA (tRNA) molecules of RNA that serve to bring amino acids to a growing polypeptide strand and properly place them into the sequence

translation process of producing a protein from the nucleotide sequence code of an mRNA transcript

triplet consecutive sequence of three nucleotides on a DNA molecule that, when transcribed into an mRNA codon, corresponds to a particular amino acid

unipotent describes the condition of being committed to a single specialized cell type

vesicle membrane-bound structure that contains materials within or outside of the cell

Chapter Review

3.1 The Cell Membrane

The cell membrane provides a barrier around the cell, separating its internal components from the extracellular environment. It is composed of a phospholipid bilayer, with hydrophobic internal lipid "tails" and hydrophilic external phosphate "heads." Various membrane proteins are scattered throughout the bilayer, both inserted within it and attached to it peripherally. The cell membrane is selectively permeable, allowing only a limited number of materials to diffuse through its lipid bilayer. All materials that cross the membrane do so using passive (non energy-requiring) or active (energy-requiring) transport processes. During passive transport, materials move by simple diffusion or by facilitated diffusion through the membrane, down their concentration gradient. Water

3.5 Cell Growth and Division

The life of cell consists of stages that make up the cell cycle. After a cell is born, it passes through an interphase before it is ready to replicate itself and produce daughter cells. This interphase includes two gap phases (G_1 and G_2), as well as an S phase, during which its DNA is replicated in preparation for cell division. The cell cycle is under precise regulation by chemical messengers both inside and outside the cell that provide "stop" and "go" signals for movement from one phase to the next. Failures of these signals can result in cells that continue to divide uncontrollably, which can lead to cancer.

Once a cell has completed interphase and is ready for cell division, it proceeds through four separate stages of mitosis (prophase, metaphase, anaphase, and telophase). Telophase is followed by the division of the cytoplasm (cytokinesis), which generates two daughter cells. This process takes place in all normally dividing cells of the body except for the germ cells that produce eggs and sperm.

3.6 Cellular Differentiation

One of the major areas of research in biology is that of how cells specialize to assume their unique structures and functions, since all cells essentially originate from a single fertilized egg. Cell differentiation is the process of cells becoming specialized as they body develops. A stem cell is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate. While all somatic cells contain the exact same genome, different cell types only express some of those genes at any given time. These differences in gene expression ultimately dictate a cell's unique morphological and physiological characteristics. The primary mechanism that determines which genes will be expressed and which ones will not is through the use of different transcription factor proteins, which bind to DNA and promote or hinder the transcription of different genes. Through the action of these transcription factors, cells specialize into one of hundreds of different cell types in the human body.

Interactive Link Questions

1. Visit this link (http://openstax.org/l/diffusion) to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?
2. Watch this video (http://openstax.org/l/endomembrane1) to learn about the endomembrane system, which includes the rough and smooth ER and the Golgi body as well as lysosomes and vesicles. What is the primary role of the endomembrane system?
3. Watch this video (http://openstax.org/l/DNArep) to learn about DNA replication. DNA replication proceeds simultaneously at several sites on the same molecule. What separates the base pair at the start of DNA replication?
4. Watch this video (http://openstax.org/l/ribosome) to learn about ribosomes. The ribosome binds to the mRNA molecule to start translation of its code into a protein. What happens to the small and large ribosomal subunits at the end of translation?
5. Visit this link (http://openstax.org/l/mitosis) to learn about mitosis. Mitosis results in two identical diploid cells. What structures form during prophase?

Review Questions

6. Because they are embedded within the membrane, ion channels are examples of _____.
   a. receptor proteins
   b. integral proteins
   c. peripheral proteins
   d. glycoproteins
7. The diffusion of substances within a solution tends to move those substances _____ their _____ gradient.
   a. up; electrical
   b. up; electrochemical
   c. down; pressure
   d. down; concentration

22. How many "letters" of an RNA molecule, in sequence, does it take to provide the code for a single amino acid?
   a. 1
   b. 2
   c. 3
   d. 4

23. Which of the following is *not* made out of RNA?
   a. the carriers that shuffle amino acids to a growing polypeptide strand
   b. the ribosome
   c. the messenger molecule that provides the code for protein synthesis
   d. the intron

24. Which of the following phases is characterized by preparation for DNA synthesis?
   a. G_0
   b. G_1
   c. G_2
   d. S

25. A mutation in the gene for a cyclin protein might result in which of the following?
   a. a cell with additional genetic material than normal
   b. cancer
   c. a cell with less genetic material than normal
   d. any of the above

26. What is a primary function of tumor suppressor genes?
   a. stop all cells from dividing
   b. stop certain cells from dividing
   c. help oncogenes produce oncoproteins
   d. allow the cell to skip certain phases of the cell cycle

27. Arrange the following terms in order of increasing specialization: oligopotency, pleuripotency, unipotency, multipotency.
   a. multipotency, pleuripotency, oligopotency, unipotency
   b. pleuripotency, oligopotency, multipotency unipotency
   c. oligopotency, pleuripotency, unipotency, multipotency
   d. pleuripotency, multipotency, oligopotency, unipotency

28. Which type of stem cell gives rise to red and white blood cells?
   a. endothelial
   b. epithelial
   c. hematopoietic
   d. mesenchymal

29. What multipotent stem cells from children sometimes banked by parents?
   a. fetal stem cells
   b. embryonic stem cells
   c. cells from the umbilical cord and from baby teeth
   d. hematopoietic stem cells from red and white blood cells

Critical Thinking Questions

30. What materials can easily diffuse through the lipid bilayer, and why?

31. Why is receptor-mediated endocytosis said to be more selective than phagocytosis or pinocytosis?

32. What do osmosis, diffusion, filtration, and the movement of ions away from like charge all have in common? In what way do they differ?

33. Explain why the structure of the ER, mitochondria, and Golgi apparatus assist their respective functions.

34. Compare and contrast lysosomes with peroxisomes: name at least two similarities and one difference.

35. Explain in your own words why DNA replication is said to be "semiconservative"?

36. Why is it important that DNA replication take place before cell division? What would happen if cell division of a body cell took place without DNA replication, or when DNA replication was incomplete?

37. Briefly explain the similarities between transcription and DNA replication.

38. Contrast transcription and translation. Name at least three differences between the two processes.

39. What would happen if anaphase proceeded even though the sister chromatids were not properly attached to their respective microtubules and lined up at the metaphase plate?

40. What are cyclins and cyclin-dependent kinases, and how do they interact?

4.1 Types of Tissues

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the four main tissue types
- Discuss the functions of each tissue type
- Relate the structure of each tissue type to their function
- Discuss the embryonic origin of tissue
- Identify the three major germ layers
- Identify the main types of tissue membranes

The term **tissue** is used to describe a group of cells found together in the body. The cells within a tissue share a common embryonic origin. Microscopic observation reveals that the cells in a tissue share morphological features and are arranged in an orderly pattern that achieves the tissue's functions. From the evolutionary perspective, tissues appear in more complex organisms. For example, multicellular protists, ancient eukaryotes, do not have cells organized into tissues.

Although there are many types of cells in the human body, they are organized into four broad categories of tissues: epithelial, connective, muscle, and nervous. Each of these categories is characterized by specific functions that contribute to the overall health and maintenance of the body. A disruption of the structure is a sign of injury or disease. Such changes can be detected through **histology**, the microscopic study of tissue appearance, organization, and function.

The Four Types of Tissues

Epithelial tissue, also referred to as epithelium, refers to the sheets of cells that cover exterior surfaces of the body, line internal cavities and passageways, and form certain glands. **Connective tissue**, as its name implies, binds the cells and organs of the body together and functions in the protection, support, and integration of all parts of the body. **Muscle tissue** is excitable, responding to stimulation and contracting to provide movement, and occurs as three major types: skeletal (voluntary) muscle, smooth muscle, and cardiac muscle in the heart. **Nervous tissue** is also excitable, allowing the propagation of electrochemical signals in the form of nerve impulses that communicate between different regions of the body (Figure 4.2).

The next level of organization is the organ, where several types of tissues come together to form a working unit. Just as knowing the structure and function of cells helps you in your study of tissues, knowledge of tissues will help you understand how organs function. The epithelial and connective tissues are discussed in detail in this chapter. Muscle and nervous tissues will be discussed only briefly in this chapter.

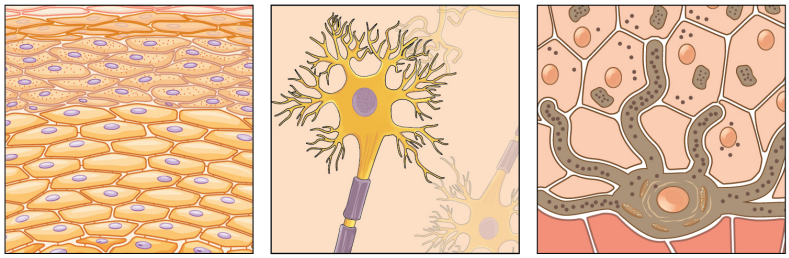
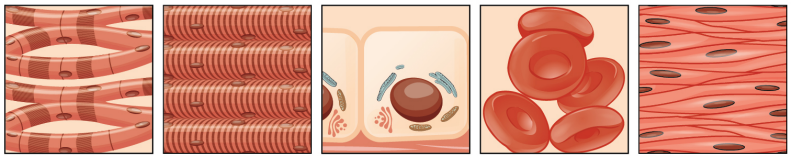
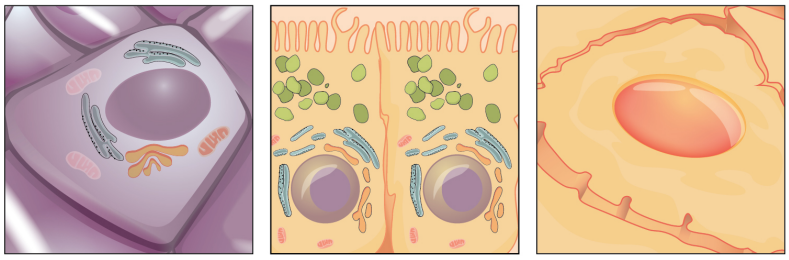
Germ Layer	Gives rise to:
Ectoderm	Epidermis, glands on skin, some cranial bones, pituitary and adrenal medulla, the nervous system, the mouth between cheek and gums, the anus  Skin cells Neurons Pigment cell
Mesoderm	Connective tissues proper, bone, cartilage, blood, endothelium of blood vessels, muscle, synovial membranes, serous membranes lining body cavities, kidneys, lining of gonads  Cardiac muscle Skeletal muscle Tubule cell of kidney Red blood cells Smooth muscle
Endoderm	Lining of airways and digestive system except the mouth and distal part of digestive system (rectum and anal canal); glands (digestive glands, endocrine glands, adrenal cortex)  Lung cell Thyroid cell Pancreatic cell

FIGURE 4.3 **Embryonic Origin of Tissues and Major Organs**

INTERACTIVE LINK

View this slideshow (http://openstax.org/l/stemcells) to learn more about stem cells. How do somatic stem cells differ from embryonic stem cells?

Tissue Membranes

A **tissue membrane** is a thin layer or sheet of cells that covers the outside of the body (for example, skin), the organs (for example, pericardium), internal passageways that lead to the exterior of the body (for example, mucosa of stomach), and the lining of the moveable joint cavities. There are two basic types of tissue membranes: connective tissue and epithelial membranes (Figure 4.4).

glands, covers the epithelial layer. The underlying connective tissue, called the **lamina propria** (literally "own layer"), help support the fragile epithelial layer.

A **serous membrane** is an epithelial membrane composed of mesodermally derived epithelium called the mesothelium that is supported by connective tissue. These membranes line the coelomic cavities of the body, that is, those cavities that do not open to the outside, and they cover the organs located within those cavities. They are essentially membranous bags, with mesothelium lining the inside and connective tissue on the outside. Serous fluid secreted by the cells of the thin squamous mesothelium lubricates the membrane and reduces abrasion and friction between organs. Serous membranes are identified according locations. Three serous membranes line the thoracic cavity; the two pleura that cover the lungs and the pericardium that covers the heart. A fourth, the peritoneum, is the serous membrane in the abdominal cavity that covers abdominal organs and forms double sheets of mesenteries that suspend many of the digestive organs.

The skin is an epithelial membrane also called the **cutaneous membrane**. It is a stratified squamous epithelial membrane resting on top of connective tissue. The apical surface of this membrane is exposed to the external environment and is covered with dead, keratinized cells that help protect the body from desiccation and pathogens.

4.2 Epithelial Tissue

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the structure and function of epithelial tissue
- Distinguish between tight junctions, anchoring junctions, and gap junctions
- Distinguish between simple epithelia and stratified epithelia, as well as between squamous, cuboidal, and columnar epithelia
- Describe the structure and function of endocrine and exocrine glands and their respective secretions

Most epithelial tissues are essentially large sheets of cells covering all the surfaces of the body exposed to the outside world and lining the outside of organs. Epithelium also forms much of the glandular tissue of the body. Skin is not the only area of the body exposed to the outside. Other areas include the airways, the digestive tract, as well as the urinary and reproductive systems, all of which are lined by an epithelium. Hollow organs and body cavities that do not connect to the exterior of the body, which includes, blood vessels and serous membranes, are lined by endothelium (plural = endothelia), which is a type of epithelium.

Epithelial cells derive from all three major embryonic layers. The epithelia lining the skin, parts of the mouth and nose, and the anus develop from the ectoderm. Cells lining the airways and most of the digestive system originate in the endoderm. The epithelium that lines vessels in the lymphatic and cardiovascular system derives from the mesoderm and is called an endothelium.

All epithelia share some important structural and functional features. This tissue is highly cellular, with little or no extracellular material present between cells. Adjoining cells form a specialized intercellular connection between their cell membranes called a **cell junction**. The epithelial cells exhibit polarity with differences in structure and function between the exposed or **apical** facing surface of the cell and the basal surface close to the underlying body structures. The **basal lamina**, a mixture of glycoproteins and collagen, provides an attachment site for the epithelium, separating it from underlying connective tissue. The basal lamina attaches to a **reticular lamina**, which is secreted by the underlying connective tissue, forming a **basement membrane** that helps hold it all together.

Epithelial tissues are nearly completely avascular. For instance, no blood vessels cross the basement membrane to enter the tissue, and nutrients must come by diffusion or absorption from underlying tissues or the surface. Many epithelial tissues are capable of rapidly replacing damaged and dead cells. Sloughing off of damaged or dead cells is a characteristic of surface epithelium and allows our airways and digestive tracts to rapidly replace damaged cells with new cells.

Generalized Functions of Epithelial Tissue

Epithelial tissues provide the body's first line of protection from physical, chemical, and biological wear and tear. The cells of an epithelium act as gatekeepers of the body controlling permeability and allowing selective transfer of materials across a physical barrier. All substances that enter the body must cross an epithelium. Some epithelia

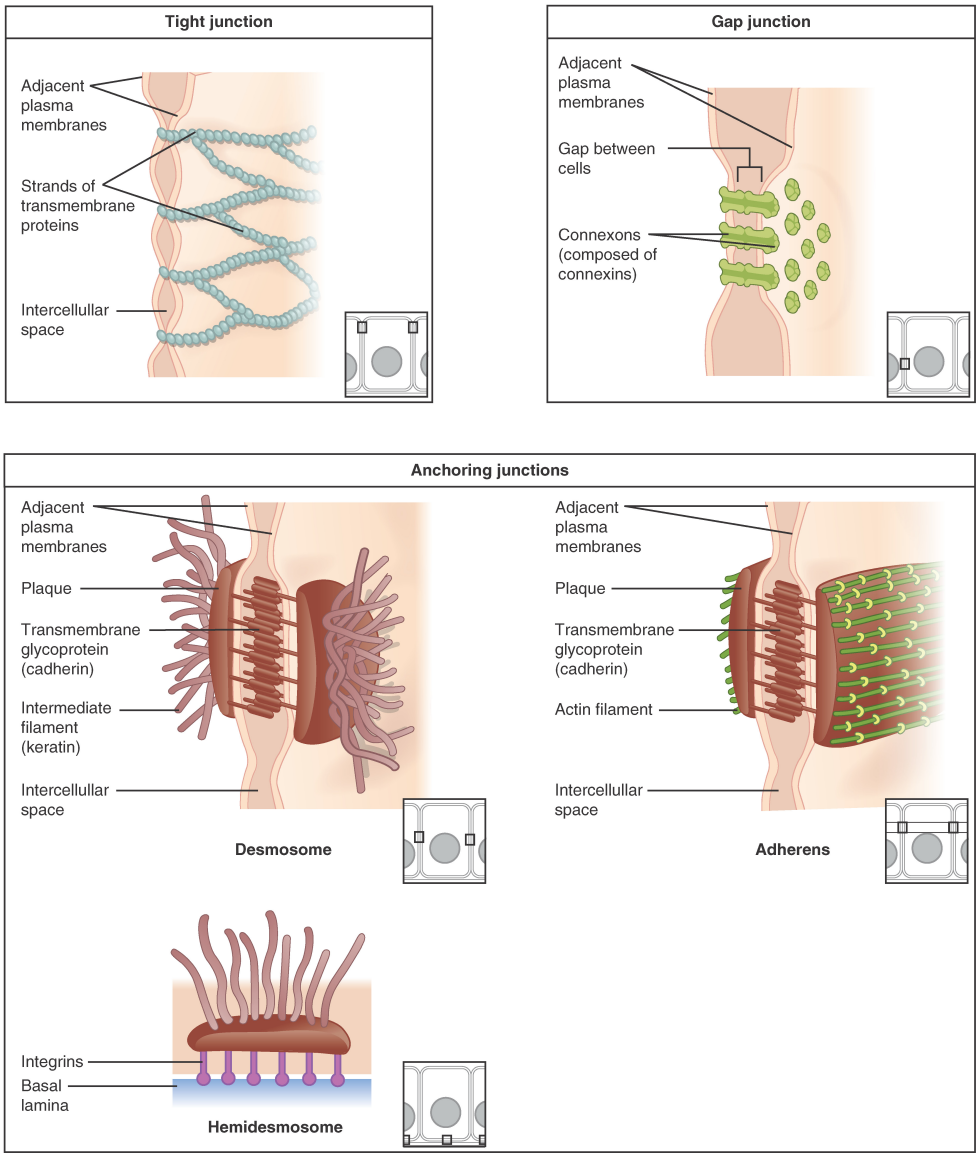


FIGURE 4.5 Types of Cell Junctions The three basic types of cell-to-cell junctions are tight junctions, gap junctions, and anchoring junctions.

At one end of the spectrum is the **tight junction**, which separates the cells into apical and basal compartments. When two adjacent epithelial cells form a tight junction, there is no extracellular space between them and the movement of substances through the extracellular space between the cells is blocked. This enables the epithelia to act as selective barriers. An **anchoring junction** includes several types of cell junctions that help stabilize epithelial tissues. Anchoring junctions are common on the lateral and basal surfaces of cells where they provide strong and flexible connections. There are three types of anchoring junctions: desmosomes, hemidesmosomes, and adherens. Desmosomes occur in patches on the membranes of cells. The patches are structural proteins on the inner surface of the cell's membrane. The adhesion molecule, cadherin, is embedded in these patches and projects through the cell membrane to link with the cadherin molecules of adjacent cells. These connections are especially important in holding cells together. Hemidesmosomes, which look like half a desmosome, link cells to the extracellular matrix, for example, the basal lamina. While similar in appearance to desmosomes, they include the adhesion proteins called integrins rather than cadherins. Adherens junctions use either cadherins or integrins depending on whether they are linking to other cells or matrix. The junctions are characterized by the presence of the contractile protein actin located on the cytoplasmic surface of the cell membrane. The actin can connect isolated patches or form a belt-like structure inside the cell. These junctions influence the shape and folding of the epithelial tissue.

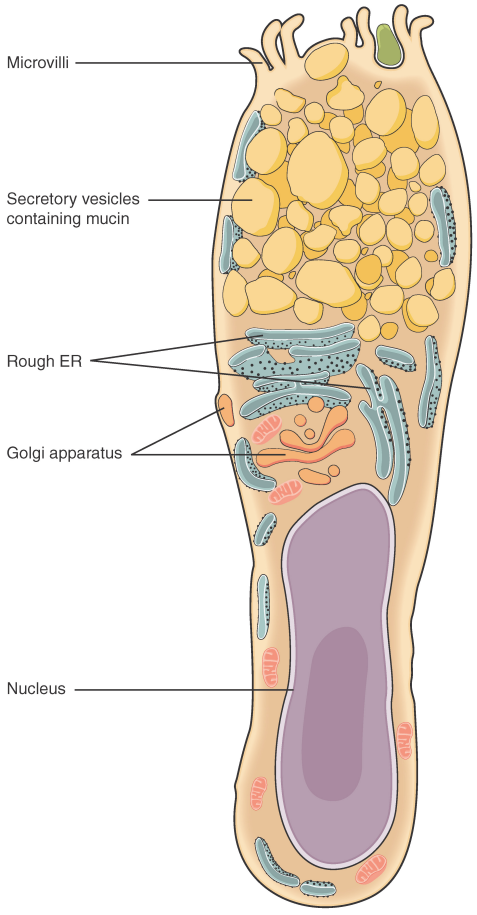
In contrast with the tight and anchoring junctions, a **gap junction** forms an intercellular passageway between the

are observed in the lining of the kidney tubules and in the ducts of glands.

In **simple columnar epithelium**, the nucleus of the tall column-like cells tends to be elongated and located in the basal end of the cells. Like the cuboidal epithelia, this epithelium is active in the absorption and secretion of molecules. Simple columnar epithelium forms the lining of some sections of the digestive system and parts of the female reproductive tract. Ciliated columnar epithelium is composed of simple columnar epithelial cells with cilia on their apical surfaces. These epithelial cells are found in the lining of the fallopian tubes and parts of the respiratory system, where the beating of the cilia helps remove particulate matter.

Pseudostratified columnar epithelium is a type of epithelium that appears to be stratified but instead consists of a single layer of irregularly shaped and differently sized columnar cells. In pseudostratified epithelium, nuclei of neighboring cells appear at different levels rather than clustered in the basal end. The arrangement gives the appearance of stratification; but in fact all the cells are in contact with the basal lamina, although some do not reach the apical surface. Pseudostratified columnar epithelium is found in the respiratory tract, where some of these cells have cilia.

Both simple and pseudostratified columnar epithelia are heterogeneous epithelia because they include additional types of cells interspersed among the epithelial cells. For example, a **goblet cell** is a mucous-secreting unicellular "gland" interspersed between the columnar epithelial cells of mucous membranes (Figure 4.7).



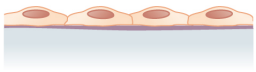
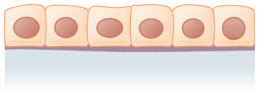
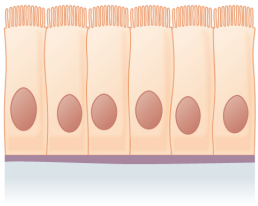
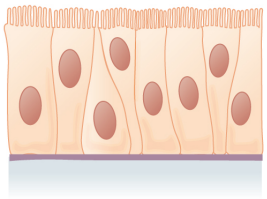
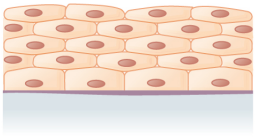
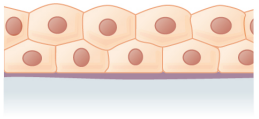
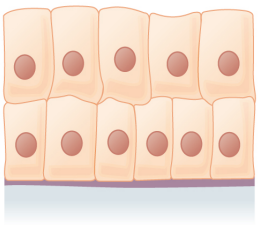
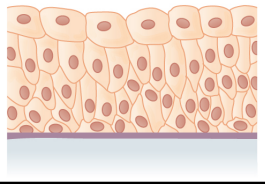
Cells	Location	Function
Simple squamous epithelium 	Air sacs of lungs and the lining of the heart, blood vessels, and lymphatic vessels	Allows materials to pass through by diffusion and filtration, and secretes lubricating substance
Simple cuboidal epithelium 	In ducts and secretory portions of small glands and in kidney tubules	Secretes and absorbs
Simple columnar epithelium 	Ciliated tissues are in larger bronchioles, uterine tubes, and uterus; smooth (nonciliated tissues) are in the digestive tract, bladder	Absorbs; it also secretes mucus and enzymes
Pseudostratified columnar epithelium 	Ciliated tissue lines the bronchi, trachea, and much of the upper respiratory tract	Secretes mucus; ciliated tissue moves mucus
Stratified squamous epithelium 	Lines the esophagus, mouth, and vagina	Protects against abrasion
Stratified cuboidal epithelium 	Sweat glands, salivary glands, and the mammary glands	Protective tissue
Stratified columnar epithelium 	The male and female urethrae and the ducts of some glands	Secretes and protects
Transitional epithelium 	Lines the bladder, urethra, and the ureters	Allows the urinary organs to expand and stretch

FIGURE 4.8 Summary of Epithelial Tissue Cells

INTERACTIVE LINK

Watch this video (http://openstax.org/l/etissues) to find out more about the anatomy of epithelial tissues. Where in the body would one find non-keratinizing stratified squamous epithelium?

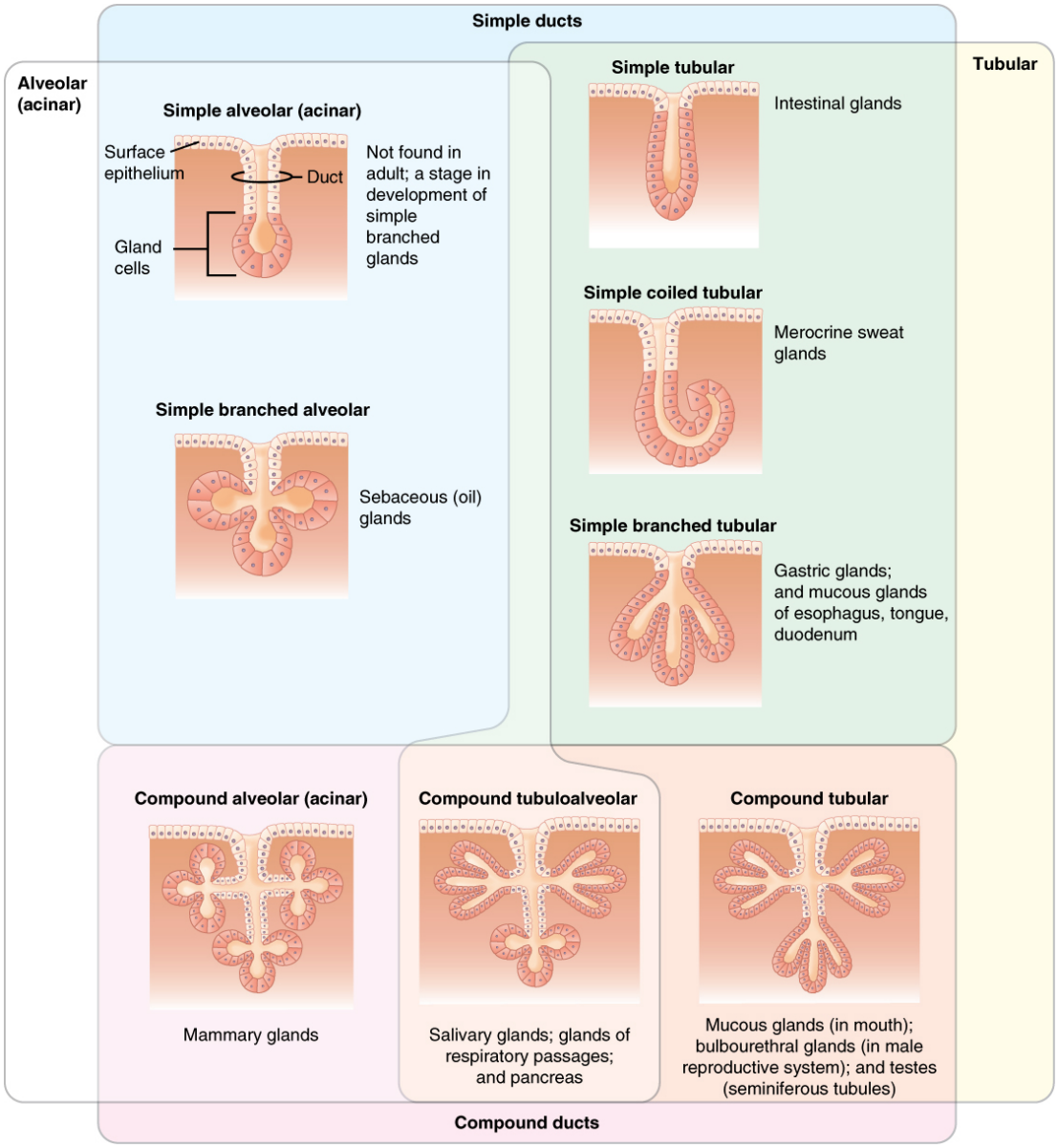


FIGURE 4.9 Types of Exocrine Glands Exocrine glands are classified by their structure.

Methods and Types of Secretion

Exocrine glands can be classified by their mode of secretion and the nature of the substances released, as well as by the structure of the glands and shape of ducts (Figure 4.10). **Merocrine secretion** is the most common type of exocrine secretion. The secretions are enclosed in vesicles that move to the apical surface of the cell where the contents are released by exocytosis. For example, watery mucous containing the glycoprotein mucin, a lubricant that offers some pathogen protection is a merocrine secretion. The eccrine glands that produce and secrete sweat are another example.

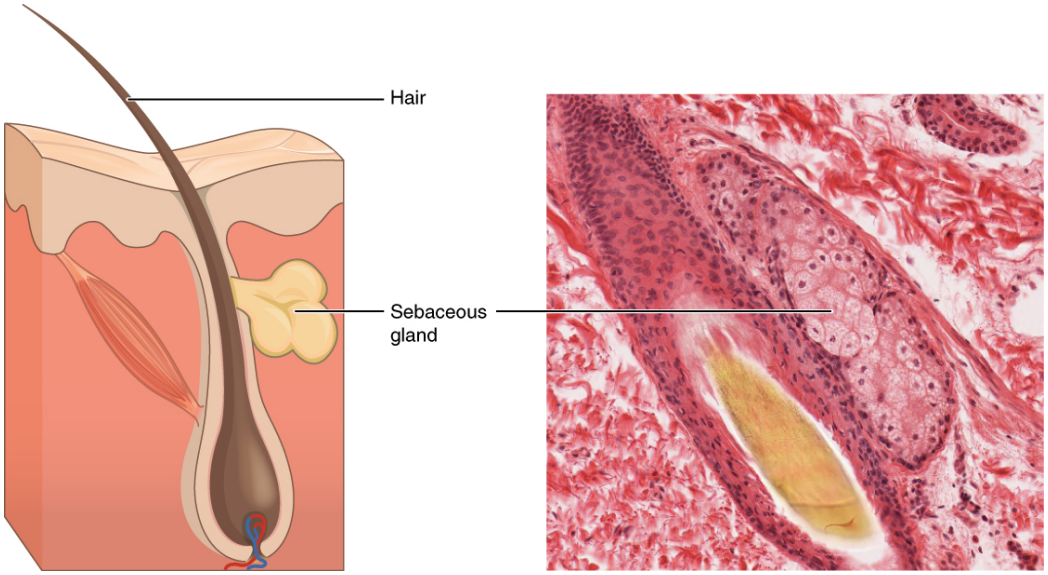


FIGURE 4.11 Sebaceous Glands These glands secrete oils that lubricate and protect the skin. They are holocrine glands and they are destroyed after releasing their contents. New glandular cells form to replace the cells that are lost. LM × 400. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Glands are also named after the products they produce. The **serous gland** produces watery, blood-plasma-like secretions rich in enzymes such as alpha amylase, whereas the **mucous gland** releases watery to viscous products rich in the glycoprotein mucin. Both serous and mucous glands are common in the salivary glands of the mouth. Mixed exocrine glands contain both serous and mucous glands and release both types of secretions.

4.3 Connective Tissue Supports and Protects

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify and distinguish between the types of connective tissue: proper, supportive, and fluid
- Explain the functions of connective tissues

As may be obvious from its name, one of the major functions of connective tissue is to connect tissues and organs. Unlike epithelial tissue, which is composed of cells closely packed with little or no extracellular space in between, connective tissue cells are dispersed in a **matrix**. The matrix usually includes a large amount of extracellular material produced by the connective tissue cells that are embedded within it. The matrix plays a major role in the functioning of this tissue. The major component of the matrix is a **ground substance** often crisscrossed by protein fibers. This ground substance is usually a fluid, but it can also be mineralized and solid, as in bones. Connective tissues come in a vast variety of forms, yet they typically have in common three characteristic components: cells, large amounts of amorphous ground substance, and protein fibers. The amount and structure of each component correlates with the function of the tissue, from the rigid ground substance in bones supporting the body to the inclusion of specialized cells; for example, a phagocytic cell that engulfs pathogens and also rids tissue of cellular debris.

Functions of Connective Tissues

Connective tissues perform many functions in the body, but most importantly, they support and connect other tissues; from the connective tissue sheath that surrounds muscle cells, to the tendons that attach muscles to bones, and to the skeleton that supports the positions of the body. Protection is another major function of connective tissue, in the form of fibrous capsules and bones that protect delicate organs and, of course, the skeletal system. Specialized cells in connective tissue defend the body from microorganisms that enter the body. Transport of fluid, nutrients, waste, and chemical messengers is ensured by specialized fluid connective tissues, such as blood and lymph. Adipose cells store surplus energy in the form of fat and contribute to the thermal insulation of the body.

Embryonic Connective Tissue

All connective tissues derive from the mesodermal layer of the embryo (see Figure 4.3). The first connective tissue

2012)

Cell Types

The most abundant cell in connective tissue proper is the **fibroblast**. Polysaccharides and proteins secreted by fibroblasts combine with extra-cellular fluids to produce a viscous ground substance that, with embedded fibrous proteins, forms the extra-cellular matrix. As you might expect, a **fibrocyte**, a less active form of fibroblast, is the second most common cell type in connective tissue proper.

Adipocytes are cells that store lipids as droplets that fill most of the cytoplasm. There are two basic types of adipocytes: white and brown. The brown adipocytes store lipids as many droplets, and have high metabolic activity. In contrast, white fat adipocytes store lipids as a single large drop and are metabolically less active. Their effectiveness at storing large amounts of fat is witnessed in obese individuals. The number and type of adipocytes depends on the tissue and location, and vary among individuals in the population.

The **mesenchymal cell** is a multipotent adult stem cell. These cells can differentiate into any type of connective tissue cells needed for repair and healing of damaged tissue.

The macrophage cell is a large cell derived from a monocyte, a type of blood cell, which enters the connective tissue matrix from the blood vessels. The macrophage cells are an essential component of the immune system, which is the body's defense against potential pathogens and degraded host cells. When stimulated, macrophages release cytokines, small proteins that act as chemical messengers. Cytokines recruit other cells of the immune system to infected sites and stimulate their activities. Roaming, or free, macrophages move rapidly by amoeboid movement, engulfing infectious agents and cellular debris. In contrast, fixed macrophages are permanent residents of their tissues.

The mast cell, found in connective tissue proper, has many cytoplasmic granules. These granules contain the chemical signals histamine and heparin. When irritated or damaged, mast cells release histamine, an inflammatory mediator, which causes vasodilation and increased blood flow at a site of injury or infection, along with itching, swelling, and redness you recognize as an allergic response. Like blood cells, mast cells are derived from hematopoietic stem cells and are part of the immune system.

Connective Tissue Fibers and Ground Substance

Three main types of fibers are secreted by fibroblasts: collagen fibers, elastic fibers, and reticular fibers. **Collagen fiber** is made from fibrous protein subunits linked together to form a long and straight fiber. Collagen fibers, while flexible, have great tensile strength, resist stretching, and give ligaments and tendons their characteristic resilience and strength. These fibers hold connective tissues together, even during the movement of the body.

Elastic fiber contains the protein elastin along with lesser amounts of other proteins and glycoproteins. The main property of elastin is that after being stretched or compressed, it will return to its original shape. Elastic fibers are prominent in elastic tissues found in skin and the elastic ligaments of the vertebral column.

Reticular fiber is also formed from the same protein subunits as collagen fibers; however, these fibers remain narrow and are arrayed in a branching network. They are found throughout the body, but are most abundant in the reticular tissue of soft organs, such as liver and spleen, where they anchor and provide structural support to the **parenchyma** (the functional cells, blood vessels, and nerves of the organ).

All of these fiber types are embedded in ground substance. Secreted by fibroblasts, ground substance is made of polysaccharides, specifically hyaluronic acid, and proteins. These combine to form a proteoglycan with a protein core and polysaccharide branches. The proteoglycan attracts and traps available moisture forming the clear, viscous, colorless matrix you now know as ground substance.

Loose Connective Tissue

Loose connective tissue is found between many organs where it acts both to absorb shock and bind tissues together. It allows water, salts, and various nutrients to diffuse through to adjacent or imbedded cells and tissues.

Adipose tissue consists mostly of fat storage cells, with little extracellular matrix (Figure 4.13). A large number of capillaries allow rapid storage and mobilization of lipid molecules. White adipose tissue is most abundant. It can appear yellow and owes its color to carotene and related pigments from plant food. White fat contributes mostly to lipid storage and can serve as insulation from cold temperatures and mechanical injuries. White adipose tissue can

orientation in each layer, and it is the layers themselves that are stacked at an angle. The dermis of the skin is an example of dense irregular connective tissue rich in collagen fibers. Dense irregular elastic tissues give arterial walls the strength and the ability to regain original shape after stretching (Figure 4.15).

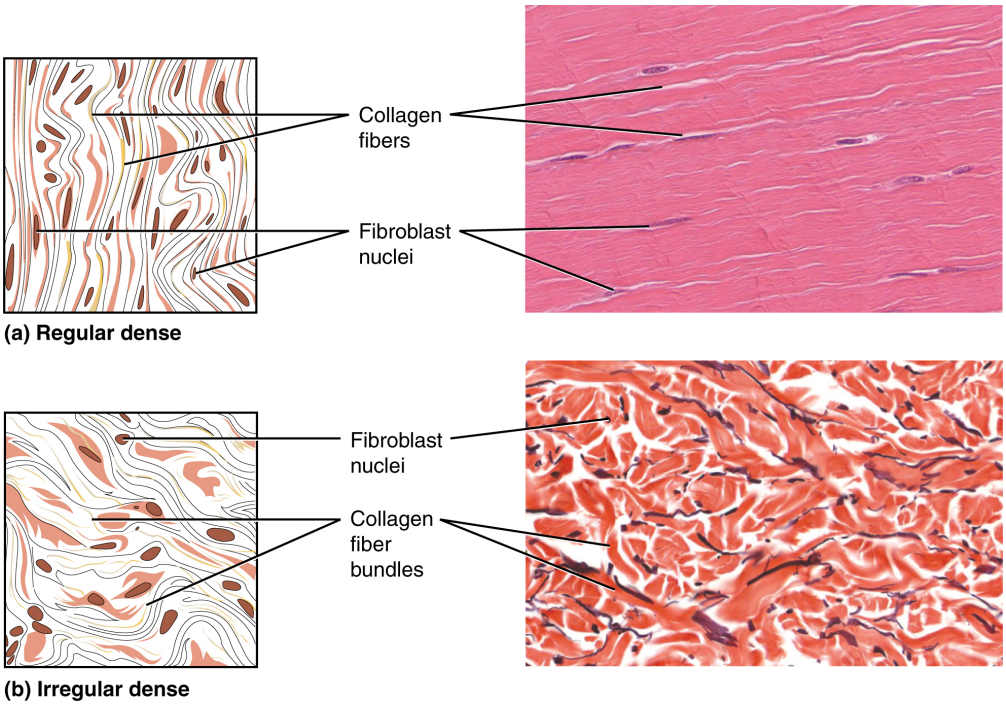


FIGURE 4.15 Dense Connective Tissue (a) Dense regular connective tissue consists of collagenous fibers packed into parallel bundles. (b) Dense irregular connective tissue consists of collagenous fibers interwoven into a mesh-like network. From top, LM × 1000, LM × 200. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Disorders of the...

Connective Tissue: Tendinitis

Your opponent stands ready as you prepare to hit the serve, but you are confident that you will smash the ball past your opponent. As you toss the ball high in the air, a burning pain shoots across your wrist and you drop the tennis racket. That dull ache in the wrist that you ignored through the summer is now an unbearable pain. The game is over for now.

After examining your swollen wrist, the doctor in the emergency room announces that you have developed wrist tendinitis. She recommends icing the tender area, taking non-steroidal anti-inflammatory medication to ease the pain and to reduce swelling, and complete rest for a few weeks. She interrupts your protests that you cannot stop playing. She issues a stern warning about the risk of aggravating the condition and the possibility of surgery. She consoles you by mentioning that well known tennis players such as Venus and Serena Williams and Rafael Nadal have also suffered from tendinitis related injuries.

What is tendinitis and how did it happen? Tendinitis is the inflammation of a tendon, the thick band of fibrous connective tissue that attaches a muscle to a bone. The condition causes pain and tenderness in the area around a joint. On rare occasions, a sudden serious injury will cause tendinitis. Most often, the condition results from repetitive motions over time that strain the tendons needed to perform the tasks.

Persons whose jobs and hobbies involve performing the same movements over and over again are often at the greatest risk of tendinitis. You hear of tennis and golfer's elbow, jumper's knee, and swimmer's shoulder. In all cases, overuse of the joint causes a microtrauma that initiates the inflammatory response. Tendinitis is routinely diagnosed through a clinical examination. In case of severe pain, X-rays can be examined to rule out the possibility of a bone injury. Severe cases of tendinitis can even tear loose a tendon. Surgical repair of a tendon is painful. Connective tissue in the tendon does not have abundant blood supply and heals slowly.

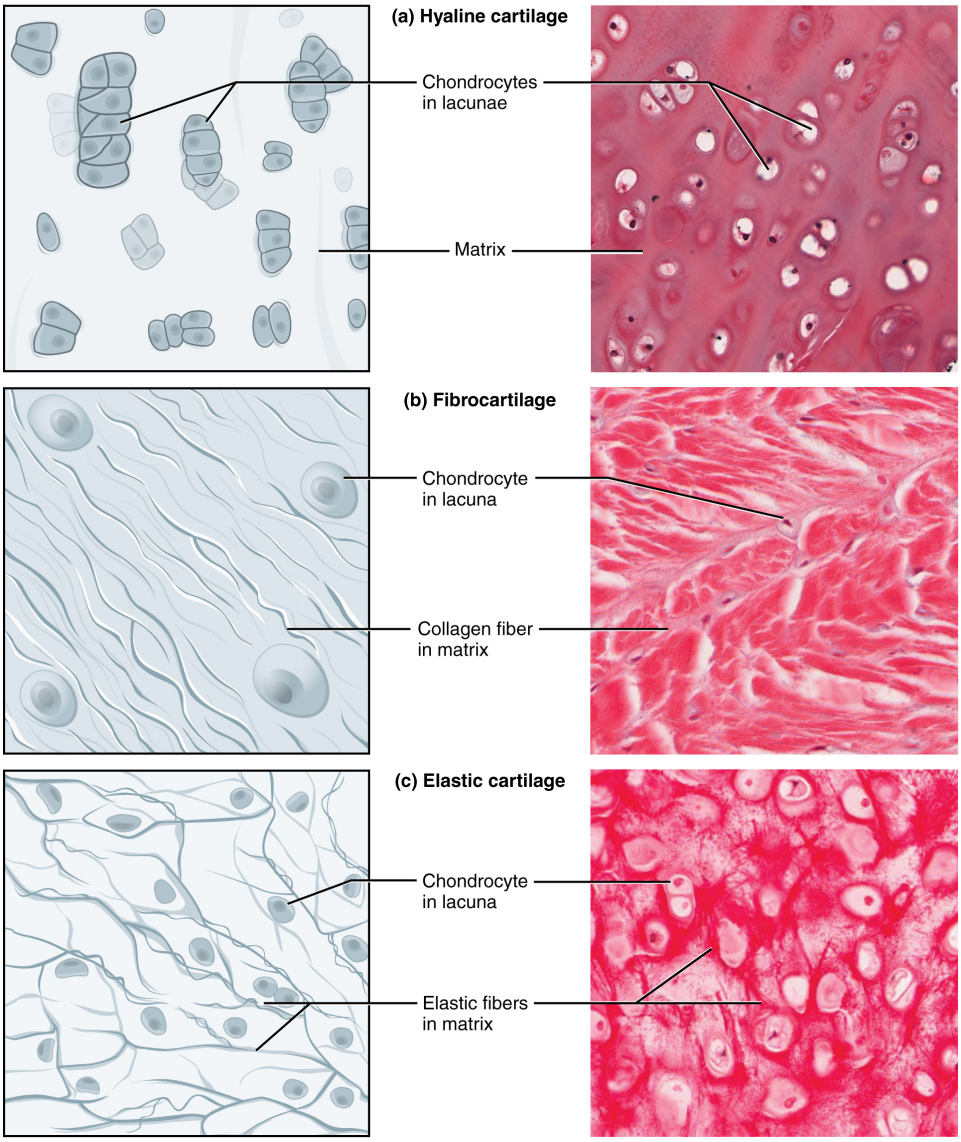


FIGURE 4.16 Types of Cartilage Cartilage is a connective tissue consisting of collagenous fibers embedded in a firm matrix of chondroitin sulfates. (a) Hyaline cartilage provides support with some flexibility. The example is from dog tissue. (b) Fibrocartilage provides some compressibility and can absorb pressure. (c) Elastic cartilage provides firm but elastic support. From top, LM × 300, LM × 1200, LM × 1016. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Bone

Bone is the hardest connective tissue. It provides protection to internal organs and supports the body. Bone's rigid extracellular matrix contains mostly collagen fibers embedded in a mineralized ground substance containing hydroxyapatite, a form of calcium phosphate. Both components of the matrix, organic and inorganic, contribute to the unusual properties of bone. Without collagen, bones would be brittle and shatter easily. Without mineral crystals, bones would flex and provide little support. Osteocytes, bone cells like chondrocytes, are located within lacunae. The histology of transverse tissue from long bone shows a typical arrangement of osteocytes in concentric circles around a central canal. Bone is a highly vascularized tissue. Unlike cartilage, bone tissue can recover from injuries in a relatively short time.

Cancellous bone looks like a sponge under the microscope and contains empty spaces between trabeculae, or arches of bone proper. It is lighter than compact bone and found in the interior of some bones and at the end of long bones. Compact bone is solid and has greater structural strength.

Fluid Connective Tissue

Blood and lymph are fluid connective tissues. Cells circulate in a liquid extracellular matrix. The formed elements

Comparison of Structure and Properties of Muscle Tissue Types

Tissue	Histology	Function	Location
Skeletal	Long cylindrical fiber, striated, many peripherally located nuclei	Voluntary movement, produces heat, protects organs	Attached to bones and around entrance points to body (e.g., mouth, anus)
Cardiac	Short, branched, striated, single central nucleus	Contracts to pump blood	Heart
Smooth	Short, spindle-shaped, no evident striation, single nucleus in each fiber	Involuntary movement, moves food, involuntary control of respiration, moves secretions, regulates flow of blood in arteries by contraction	Walls of major organs and passageways

TABLE 4.2

Skeletal muscle is attached to bones and its contraction makes possible locomotion, facial expressions, posture, and other voluntary movements of the body. Forty percent of your body mass is made up of skeletal muscle. Skeletal muscles generate heat as a byproduct of their contraction and thus participate in thermal homeostasis. Shivering is an involuntary contraction of skeletal muscles in response to perceived lower than normal body temperature. The muscle cell, or **myocyte**, develops from myoblasts derived from the mesoderm. Myocytes and their numbers remain relatively constant throughout life. Skeletal muscle tissue is arranged in bundles surrounded by connective tissue. Under the light microscope, muscle cells appear striated with many nuclei squeezed along the membranes. The **striation** is due to the regular alternation of the contractile proteins actin and myosin, along with the structural proteins that couple the contractile proteins to connective tissues. The cells are multinucleated as a result of the fusion of the many myoblasts that fuse to form each long muscle fiber.

Cardiac muscle forms the contractile walls of the heart. The cells of cardiac muscle, known as cardiomyocytes, also appear striated under the microscope. Unlike skeletal muscle fibers, cardiomyocytes are single cells typically with a single centrally located nucleus. A principal characteristic of cardiomyocytes is that they contract on their own intrinsic rhythms without any external stimulation. Cardiomyocyte attach to one another with specialized cell junctions called intercalated discs. Intercalated discs have both anchoring junctions and gap junctions. Attached cells form long, branching cardiac muscle fibers that are, essentially, a mechanical and electrochemical syncytium allowing the cells to synchronize their actions. The cardiac muscle pumps blood through the body and is under involuntary control. The attachment junctions hold adjacent cells together across the dynamic pressures changes of the cardiac cycle.

Smooth muscle tissue contraction is responsible for involuntary movements in the internal organs. It forms the contractile component of the digestive, urinary, and reproductive systems as well as the airways and arteries. Each cell is spindle shaped with a single nucleus and no visible striations (Figure 4.18).

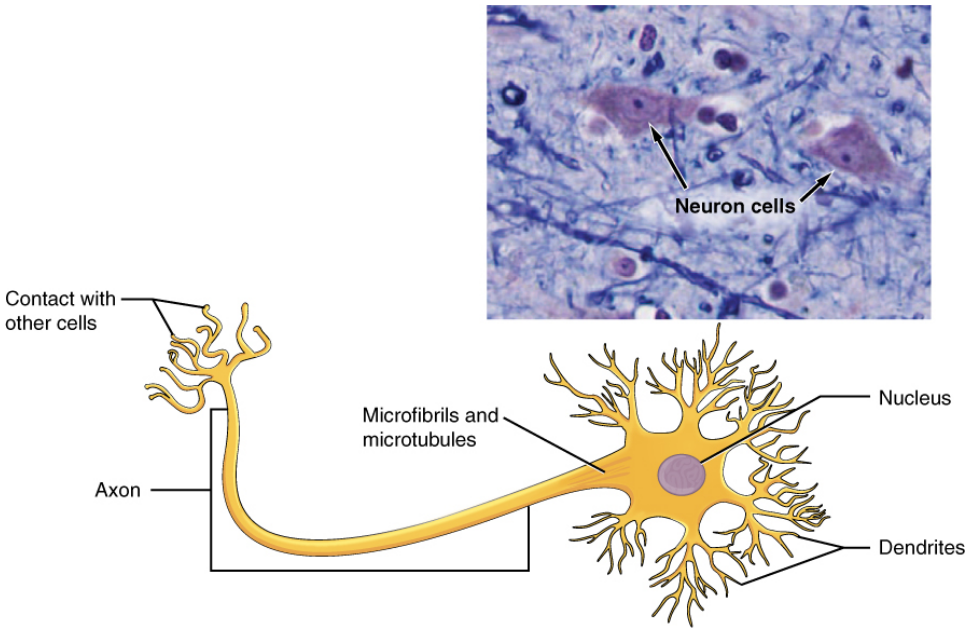


FIGURE 4.19 The Neuron The cell body of a neuron, also called the soma, contains the nucleus and mitochondria. The dendrites transfer the nerve impulse to the soma. The axon carries the action potential away to another excitable cell. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

Follow this link (http://openstax.org/l/nobel) to learn more about nervous tissue. What are the main parts of a nerve cell?

Neurons display distinctive morphology, well suited to their role as conducting cells, with three main parts. The cell body includes most of the cytoplasm, the organelles, and the nucleus. Dendrites branch off the cell body and appear as thin extensions. A long "tail," the axon, extends from the neuron body and can be wrapped in an insulating layer known as **myelin**, which is formed by accessory cells. The synapse is the gap between nerve cells, or between a nerve cell and its target, for example, a muscle or a gland, across which the impulse is transmitted by chemical compounds known as neurotransmitters. Neurons categorized as multipolar neurons have several dendrites and a single prominent axon. Bipolar neurons possess a single dendrite and axon with the cell body, while unipolar neurons have only a single process extending out from the cell body, which divides into a functional dendrite and into a functional axon. When a neuron is sufficiently stimulated, it generates an action potential that propagates down the axon towards the synapse. If enough neurotransmitters are released at the synapse to stimulate the next neuron or target, a response is generated.

The second class of neural cells comprises the neuroglia or glial cells, which have been characterized as having a simple support role. The word "glia" comes from the Greek word for glue. Recent research is shedding light on the more complex role of neuroglia in the function of the brain and nervous system. **Astrocyte** cells, named for their distinctive star shape, are abundant in the central nervous system. The astrocytes have many functions, including regulation of ion concentration in the intercellular space, uptake and/or breakdown of some neurotransmitters, and formation of the blood-brain barrier, the membrane that separates the circulatory system from the brain. Microglia protect the nervous system against infection but are not nervous tissue because they are related to macrophages. **Oligodendrocyte** cells produce myelin in the central nervous system (brain and spinal cord) while the **Schwann cell** produces myelin in the peripheral nervous system (Figure 4.20).

response.

After containment of an injury, the tissue repair phase starts with removal of toxins and waste products. **Clotting** (coagulation) reduces blood loss from damaged blood vessels and forms a network of fibrin proteins that trap blood cells and bind the edges of the wound together. A scab forms when the clot dries, reducing the risk of infection. Sometimes a mixture of dead leukocytes and fluid called pus accumulates in the wound. As healing progresses, fibroblasts from the surrounding connective tissues replace the collagen and extracellular material lost by the injury. Angiogenesis, the growth of new blood vessels, results in vascularization of the new tissue known as granulation tissue. The clot retracts pulling the edges of the wound together, and it slowly dissolves as the tissue is repaired. When a large amount of granulation tissue forms and capillaries disappear, a pale scar is often visible in the healed area. A **primary union** describes the healing of a wound where the edges are close together. When there is a gaping wound, it takes longer to refill the area with cells and collagen. The process called **secondary union** occurs as the edges of the wound are pulled together by what is called **wound contraction**. When a wound is more than one quarter of an inch deep, sutures (stitches) are recommended to promote a primary union and avoid the formation of a disfiguring scar. Regeneration is the addition of new cells of the same type as the ones that were injured (Figure 4.21).

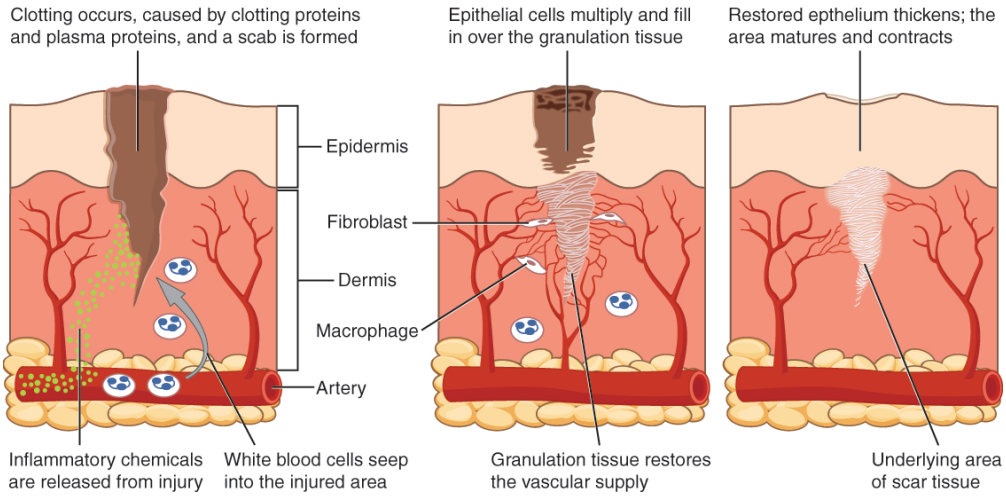


FIGURE 4.21 Tissue Healing During wound repair, collagen fibers are laid down randomly by fibroblasts that move into repair the area.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/healingskin) to see the skin healing process. What is the process and how long does it take?

Tissue and Aging

According to poet Ralph Waldo Emerson, "The surest poison is time." In fact, biology confirms that many functions of the body decline with age. All the cells, tissues, and organs are affected by senescence, with noticeable variability between individuals owing to different genetic makeup and lifestyles. The outward signs of aging are easily recognizable. The skin and other tissues become thinner and drier, reducing their elasticity, contributing to wrinkles and high blood pressure. Hair turns gray because follicles produce less melanin, the brown pigment of hair and the iris of the eye. The face looks flabby because elastic and collagen fibers decrease in connective tissue and muscle tone is lost. Glasses and hearing aids may become parts of life as the senses slowly deteriorate, all due to reduced elasticity. Overall height decreases as the bones lose calcium and other minerals. With age, fluid decreases in the fibrous cartilage disks intercalated between the vertebrae in the spine. Joints lose cartilage and stiffen. Many tissues, including those in muscles, lose mass through a process called **atrophy**. Lumps and rigidity become more widespread. As a consequence, the passageways, blood vessels, and airways become more rigid. The brain and spinal cord lose mass. Nerves do not transmit impulses with the same speed and frequency as in the past. Some loss of thought clarity and memory can accompany aging. More severe problems are not necessarily associated with the aging process and may be symptoms of underlying illness.

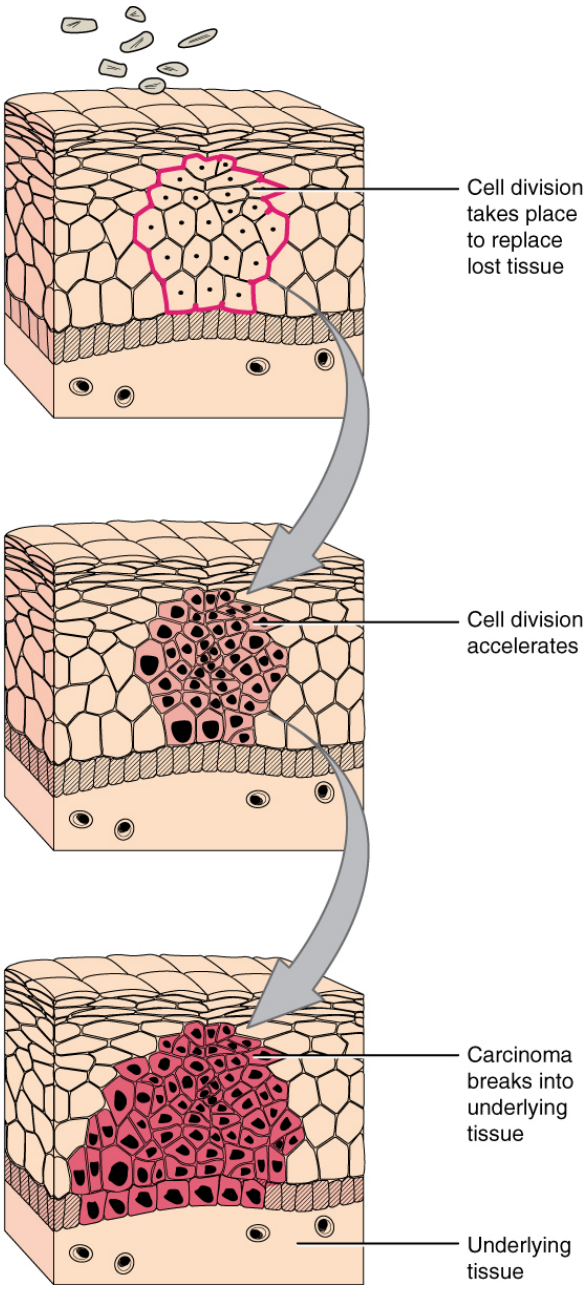


FIGURE 4.22 Development of Cancer Note the change in cell size, nucleus size, and organization in the tissue.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/tumor) to learn more about tumors. What is a tumor?

Cancer treatments vary depending on the disease's type and stage. Traditional approaches, including surgery, radiation, chemotherapy, and hormonal therapy, aim to remove or kill rapidly dividing cancer cells, but these strategies have their limitations. Depending on a tumor's location, for example, cancer surgeons may be unable to remove it. Radiation and chemotherapy are difficult, and it is often impossible to target only the cancer cells. The treatments inevitably destroy healthy tissue as well. To address this, researchers are working on pharmaceuticals that can target specific proteins implicated in cancer-associated molecular pathways.

hyaline cartilage most common type of cartilage, smooth and made of short collagen fibers embedded in a chondroitin sulfate ground substance
inflammation response of tissue to injury
lacunae (singular = lacuna) small spaces in bone or cartilage tissue that cells occupy
lamina propria areolar connective tissue underlying a mucous membrane
loose connective tissue (also, areolar tissue) type of connective tissue proper that shows little specialization with cells dispersed in the matrix
matrix extracellular material which is produced by the cells embedded in it, containing ground substance and fibers
merocrine secretion release of a substance from a gland via exocytosis
mesenchymal cell adult stem cell from which most connective tissue cells are derived
mesenchyme embryonic tissue from which connective tissue cells derive
mesoderm middle embryonic germ layer from which connective tissue, muscle tissue, and some epithelial tissue derive
mesothelium simple squamous epithelial tissue which covers the major body cavities and is the epithelial portion of serous membranes
mucous connective tissue specialized loose connective tissue present in the umbilical cord
mucous gland group of cells that secrete mucous, a thick, slippery substance that keeps tissues moist and acts as a lubricant
mucous membrane tissue membrane that is covered by protective mucous and lines tissue exposed to the outside environment
muscle tissue type of tissue that is capable of contracting and generating tension in response to stimulation; produces movement.
myelin layer of lipid inside some neuroglial cells that wraps around the axons of some neurons
myocyte muscle cells
necrosis accidental death of cells and tissues
nervous tissue type of tissue that is capable of sending and receiving impulses through electrochemical signals.
neuroglia supportive neural cells
neuron excitable neural cell that transfer nerve impulses
oligodendrocyte neuroglial cell that produces myelin in the brain
parenchyma functional cells of a gland or organ, in contrast with the supportive or connective tissue of a gland or organ
primary union condition of a wound where the wound edges are close enough to be brought together and fastened if necessary, allowing quicker and more thorough healing
pseudostratified columnar epithelium tissue that consists of a single layer of irregularly shaped and sized cells that give the appearance of multiple layers; found in ducts of certain glands and the upper respiratory tract
reticular fiber fine fibrous protein, made of collagen subunits, which cross-link to form supporting "nets" within connective tissue
reticular lamina matrix containing collagen and elastin secreted by connective tissue; a component of the basement membrane
reticular tissue type of loose connective tissue that provides a supportive framework to soft organs, such as lymphatic tissue, spleen, and the liver
Schwann cell neuroglial cell that produces myelin in the peripheral nervous system
secondary union wound healing facilitated by wound contraction
serous gland group of cells within the serous membrane that secrete a lubricating substance onto the surface
serous membrane type of tissue membrane that lines body cavities and lubricates them with serous fluid
simple columnar epithelium tissue that consists of a single layer of column-like cells; promotes secretion and absorption in tissues and organs
simple cuboidal epithelium tissue that consists of a single layer of cube-shaped cells; promotes secretion and absorption in ducts and tubules
simple squamous epithelium tissue that consists of a single layer of flat scale-like cells; promotes diffusion and filtration across surface
skeletal muscle usually attached to bone, under voluntary control, each cell is a fiber that is multinucleated and striated
smooth muscle under involuntary control, moves internal organs, cells contain a single nucleus, are spindle-shaped, and do not appear striated; each cell is a fiber
stratified columnar epithelium tissue that consists of two or more layers of column-like cells, contains glands and is found in some ducts
stratified cuboidal epithelium tissue that consists of two or more layers of cube-shaped cells, found in some ducts
stratified squamous epithelium tissue that consists of multiple layers of cells with the most apical being flat scale-like cells; protects surfaces from abrasion

are the most abundant and secrete many protein fibers, adipocytes specialize in fat storage, hematopoietic cells from the bone marrow give rise to all the blood cells, chondrocytes form cartilage, and osteocytes form bone. The extracellular matrix contains fluid, proteins, polysaccharide derivatives, and, in the case of bone, mineral crystals. Protein fibers fall into three major groups: collagen fibers that are thick, strong, flexible, and resist stretch; reticular fibers that are thin and form a supportive mesh; and elastin fibers that are thin and elastic.

The major types of connective tissue are connective tissue proper, supportive tissue, and fluid tissue. Loose connective tissue proper includes adipose tissue, areolar tissue, and reticular tissue. These serve to hold organs and other tissues in place and, in the case of adipose tissue, isolate and store energy reserves. The matrix is the most abundant feature for loose tissue although adipose tissue does not have much extracellular matrix. Dense connective tissue proper is richer in fibers and may be regular, with fibers oriented in parallel as in ligaments and tendons, or irregular, with fibers oriented in several directions. Organ capsules (collagenous type) and walls of arteries (elastic type) contain dense irregular connective tissue. Cartilage and bone are supportive tissue. Cartilage contains chondrocytes and is somewhat flexible. Hyaline cartilage is smooth and clear, covers joints, and is found in the growing portion of bones. Fibrocartilage is tough because of extra collagen fibers and forms, among other things, the intervertebral discs. Elastic cartilage can stretch and recoil to its original shape because of its high content of elastic fibers. The matrix contains very few blood vessels. Bones are made of a rigid, mineralized matrix containing calcium salts, crystals, and osteocytes lodged in lacunae. Bone tissue is highly vascularized. Cancellous bone is spongy and less solid than compact bone. Fluid tissue, for example blood and lymph, is characterized by a liquid matrix and no supporting fibers.

4.4 Muscle Tissue and Motion

The three types of muscle cells are skeletal, cardiac, and smooth. Their morphologies match their specific functions in the body. Skeletal muscle is voluntary and responds to conscious stimuli. The cells are striated and multinucleated appearing as long, unbranched cylinders. Cardiac muscle is involuntary and found only in the heart. Each cell is striated with a single nucleus and they attach to one another to form long fibers. Cells are attached to one another at intercalated disks. The cells are interconnected physically and electrochemically to act as a syncytium. Cardiac muscle cells contract autonomously and involuntarily. Smooth muscle is involuntary. Each cell is a spindle-shaped fiber and contains a single nucleus. No striations are evident because the actin and myosin filaments do not align in the cytoplasm.

4.5 Nervous Tissue Mediates Perception and Response

The most prominent cell of the nervous tissue, the neuron, is characterized mainly by its ability to receive stimuli and respond by generating an electrical signal, known as an action potential, which can travel rapidly over great distances in the body. A typical neuron displays a distinctive morphology: a large cell body branches out into short extensions called dendrites, which receive chemical signals from other neurons, and a long tail called an axon, which relays signals away from the cell to other neurons, muscles, or glands. Many axons are wrapped by a myelin sheath, a lipid derivative that acts as an insulator and speeds up the transmission of the action potential. Other cells in the nervous tissue, the neuroglia, include the astrocytes, microglia, oligodendrocytes, and Schwann cells.

4.6 Tissue Injury and Aging

Inflammation is the classic response of the body to injury and follows a common sequence of events. The area is red, feels warm to the touch, swells, and is painful. Injured cells, mast cells, and resident macrophages release chemical signals that cause vasodilation and fluid leakage in the surrounding tissue. The repair phase includes blood clotting, followed by regeneration of tissue as fibroblasts deposit collagen. Some tissues regenerate more readily than others. Epithelial and connective tissues replace damaged or dead cells from a supply of adult stem cells. Muscle and nervous tissues undergo either slow regeneration or do not repair at all.

Age affects all the tissues and organs of the body. Damaged cells do not regenerate as rapidly as in younger people. Perception of sensation and effectiveness of response are lost in the nervous system. Muscles atrophy, and bones lose mass and become brittle. Collagen decreases in some connective tissue, and joints stiffen.

17. Which connective tissue specializes in storage of fat?
   a. tendon
   b. adipose tissue
   c. reticular tissue
   d. dense connective tissue

18. Ligaments connect bones together and withstand a lot of stress. What type of connective tissue should you expect ligaments to contain?
   a. areolar tissue
   b. adipose tissue
   c. dense regular connective tissue
   d. dense irregular connective tissue

19. In adults, new connective tissue cells originate from the _____.
   a. mesoderm
   b. mesenchyme
   c. ectoderm
   d. endoderm

20. In bone, the main cells are _____.
   a. fibroblasts
   b. chondrocytes
   c. lymphocytes
   d. osteocytes

21. Striations, cylindrical cells, and multiple nuclei are observed in _____.
   a. skeletal muscle only
   b. cardiac muscle only
   c. smooth muscle only
   d. skeletal and cardiac muscles

22. The cells of muscles, myocytes, develop from _____.
   a. myoblasts
   b. endoderm
   c. fibrocytes
   d. chondrocytes

23. Skeletal muscle is composed of very hard working cells. Which organelles do you expect to find in abundance in skeletal muscle cell?
   a. nuclei
   b. striations
   c. golgi bodies
   d. mitochondria

24. The cells responsible for the transmission of the nerve impulse are _____.
   a. neurons
   b. oligodendrocytes
   c. astrocytes
   d. microglia

25. The nerve impulse travels down a(n) _____, away from the cell body.
   a. dendrite
   b. axon
   c. microglia
   d. collagen fiber

26. Which of the following central nervous system cells regulate ions, regulate the uptake and/or breakdown of some neurotransmitters, and contribute to the formation of the blood-brain barrier?
   a. microglia
   b. neuroglia
   c. oligodendrocytes
   d. astrocytes

27. Which of the following processes is not a cardinal sign of inflammation?
   a. redness
   b. heat
   c. fever
   d. swelling

28. When a mast cell reacts to an irritation, which of the following chemicals does it release?
   a. collagen
   b. histamine
   c. hyaluronic acid
   d. meylin

29. Atrophy refers to _____.
   a. loss of elasticity
   b. loss of mass
   c. loss of rigidity
   d. loss of permeability

30. Individuals can slow the rate of aging by modifying all of these lifestyle aspects except for _____.
   a. diet
   b. exercise
   c. genetic factors
   d. stress

Critical Thinking Questions

31. Identify the four types of tissue in the body, and describe the major functions of each tissue.

nerve fibers ensuring communication to and from the brain.

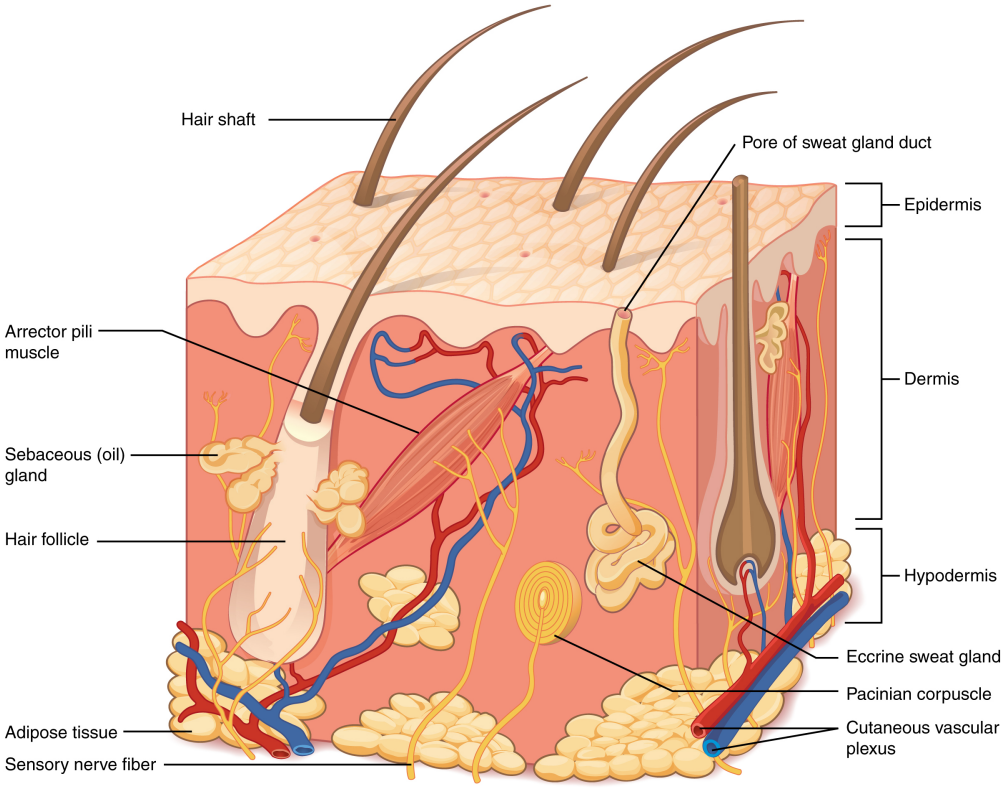


FIGURE 5.2 Layers of Skin The skin is composed of two main layers: the epidermis, made of closely packed epithelial cells, and the dermis, made of dense, irregular connective tissue that houses blood vessels, hair follicles, sweat glands, and other structures. Beneath the dermis lies the hypodermis, which is composed mainly of loose connective and fatty tissues.

INTERACTIVE LINK

The skin consists of two main layers and a closely associated layer. View this animation (http://openstax.org/l/layers) to learn more about layers of the skin. What are the basic functions of each of these layers?

The Epidermis

The **epidermis** is composed of keratinized, stratified squamous epithelium. It is made of four or five layers of epithelial cells, depending on its location in the body. It does not have any blood vessels within it (i.e., it is avascular). Skin that has four layers of cells is referred to as "thin skin." From deep to superficial, these layers are the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum. Most of the skin can be classified as thin skin. "Thick skin" is found only on the palms of the hands and the soles of the feet. It has a fifth layer, called the stratum lucidum, located between the stratum corneum and the stratum granulosum (Figure 5.3).

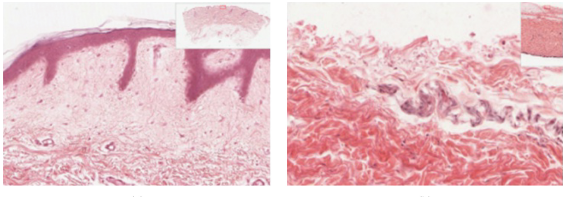


FIGURE 5.3 Thin Skin versus Thick Skin These slides show cross-sections of the epidermis and dermis of (a) thin and (b) thick skin. Note the significant difference in the thickness of the epithelial layer of the thick skin. From top, LM × 40, LM × 40. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The cells in all of the layers except the stratum basale are called keratinocytes. A **keratinocyte** is a cell that manufactures and stores the protein keratin. **Keratin** is an intracellular fibrous protein that gives hair, nails, and skin their hardness and water-resistant properties. The keratinocytes in the stratum corneum are dead and regularly slough away, being replaced by cells from the deeper layers (Figure 5.4).

that is a precursor of the keratinocytes of the epidermis. All of the keratinocytes are produced from this single layer of cells, which are constantly going through mitosis to produce new cells. As new cells are formed, the existing cells are pushed superficially away from the stratum basale. Two other cell types are found dispersed among the basal cells in the stratum basale. The first is a **Merkel cell**, which functions as a receptor and is responsible for stimulating sensory nerves that the brain perceives as touch. These cells are especially abundant on the surfaces of the hands and feet. The second is a **melanocyte**, a cell that produces the pigment melanin. **Melanin** gives hair and skin its color, and also helps protect the living cells of the epidermis from ultraviolet (UV) radiation damage.

In a growing fetus, fingerprints form where the cells of the stratum basale meet the papillae of the underlying dermal layer (papillary layer), resulting in the formation of the ridges on your fingers that you recognize as fingerprints. Fingerprints are unique to each individual and are used for forensic analyses because the patterns do not change with the growth and aging processes.

Stratum Spinosum

As the name suggests, the **stratum spinosum** is spiny in appearance due to the protruding cell processes that join the cells via a structure called a **desmosome**. The desmosomes interlock with each other and strengthen the bond between the cells. It is interesting to note that the "spiny" nature of this layer is an artifact of the staining process. Unstained epidermis samples do not exhibit this characteristic appearance. The stratum spinosum is composed of eight to 10 layers of keratinocytes, formed as a result of cell division in the stratum basale (Figure 5.6). Interspersed among the keratinocytes of this layer is a type of dendritic cell called the **Langerhans cell**, which functions as a macrophage by engulfing bacteria, foreign particles, and damaged cells that occur in this layer.

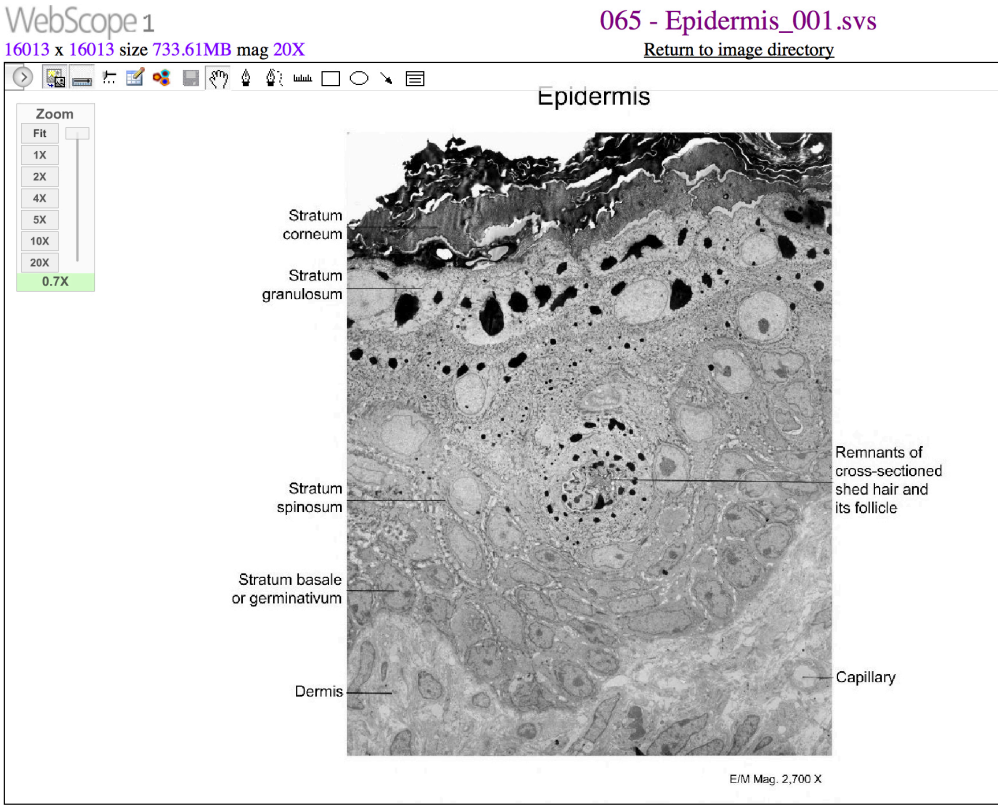


FIGURE 5.6 Cells of the Epidermis The cells in the different layers of the epidermis originate from basal cells located in the stratum basale, yet the cells of each layer are distinctively different. EM × 2700. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/basal) to explore the tissue sample in greater detail. If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

The keratinocytes in the stratum spinosum begin the synthesis of keratin and release a water-repelling glycolipid

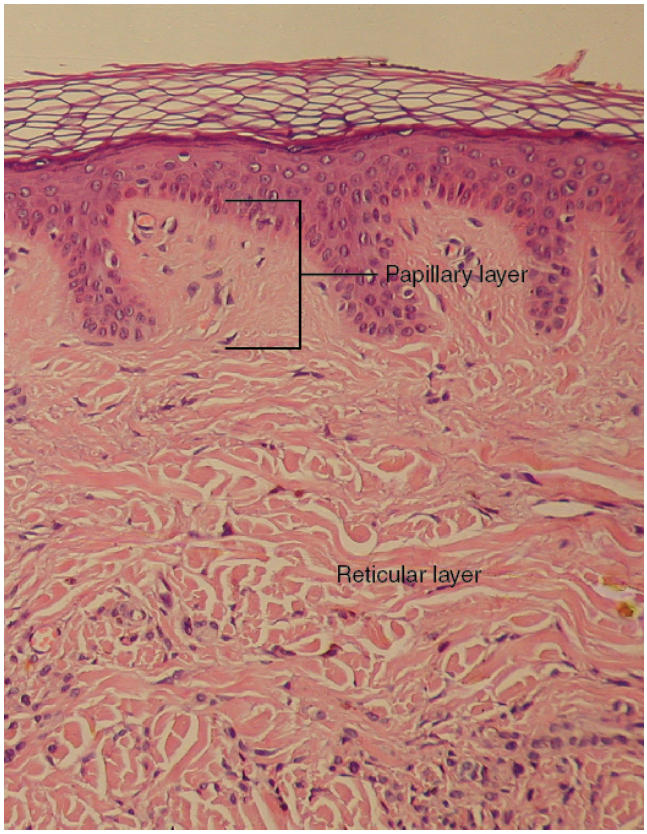


FIGURE 5.7 Layers of the Dermis This stained slide shows the two components of the dermis—the papillary layer and the reticular layer. Both are made of connective tissue with fibers of collagen extending from one to the other, making the border between the two somewhat indistinct. The dermal papillae extending into the epidermis belong to the papillary layer, whereas the dense collagen fiber bundles below belong to the reticular layer. LM × 10. (credit: modification of work by "kilbad"/Wikimedia Commons)

Papillary Layer

The **papillary layer** is made of loose, areolar connective tissue, which means the collagen and elastin fibers of this layer form a loose mesh. This superficial layer of the dermis projects into the stratum basale of the epidermis to form finger-like dermal papillae (see Figure 5.7). Within the papillary layer are fibroblasts, a small number of fat cells (adipocytes), and an abundance of small blood vessels. In addition, the papillary layer contains phagocytes, defensive cells that help fight bacteria or other infections that have breached the skin. This layer also contains lymphatic capillaries, nerve fibers, and touch receptors called the Meissner corpuscles.

Reticular Layer

Underlying the papillary layer is the much thicker **reticular layer**, composed of dense, irregular connective tissue. This layer is well vascularized and has a rich sensory and sympathetic nerve supply. The reticular layer appears reticulated (net-like) due to a tight meshwork of fibers. **Elastin fibers** provide some elasticity to the skin, enabling movement. Collagen fibers provide structure and tensile strength, with strands of collagen extending into both the papillary layer and the hypodermis. In addition, collagen binds water to keep the skin hydrated. Collagen injections and Retin-A creams help restore skin turgor by either introducing collagen externally or stimulating blood flow and repair of the dermis, respectively.

Hypodermis

The **hypodermis** (also called the subcutaneous layer or superficial fascia) is a layer directly below the dermis and serves to connect the skin to the underlying fascia (fibrous tissue) of the bones and muscles. It is not strictly a part of the skin, although the border between the hypodermis and dermis can be difficult to distinguish. The hypodermis consists of well-vascularized, loose, areolar connective tissue and adipose tissue, which functions as a mode of fat storage and provides insulation and cushioning for the integument.

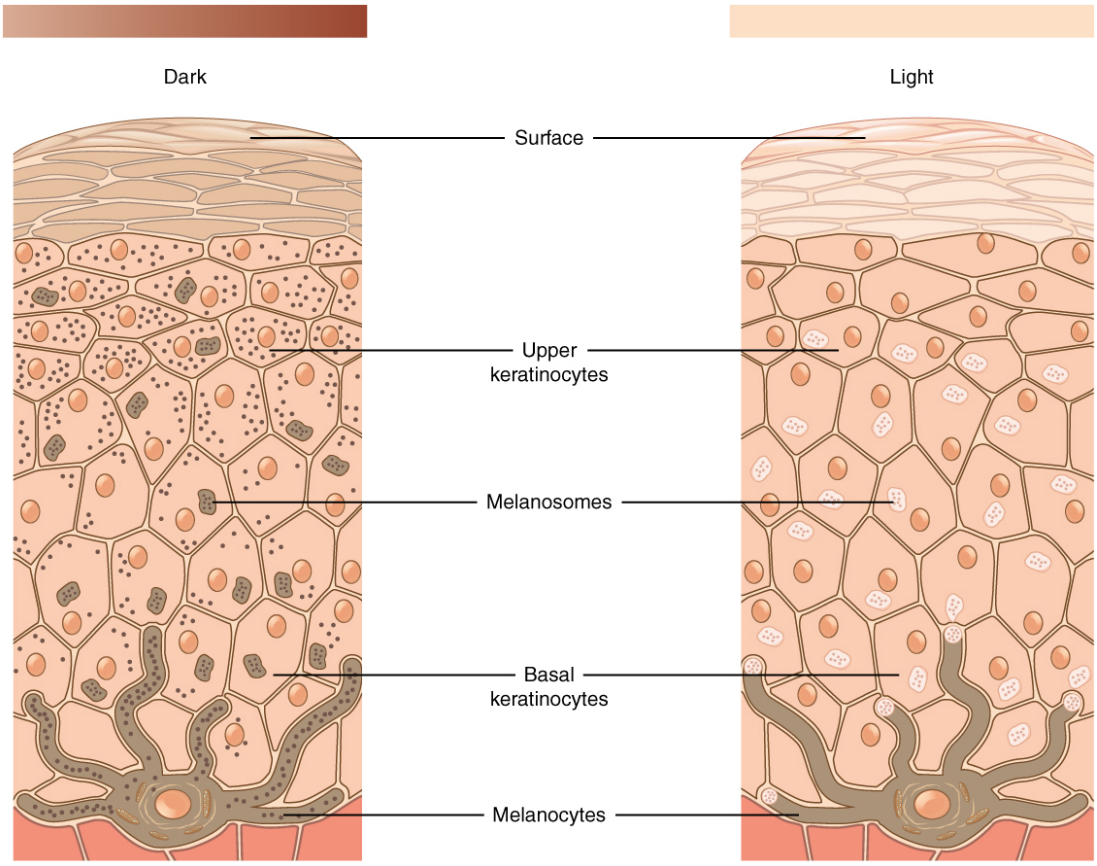


FIGURE 5.8 Skin Pigmentation The relative coloration of the skin depends of the amount of melanin produced by melanocytes in the stratum basale and taken up by keratinocytes.

Melanin occurs in two primary forms. Eumelanin exists as black and brown, whereas pheomelanin provides a red color. Dark-skinned individuals produce more melanin than those with pale skin. Exposure to the UV rays of the sun or a tanning salon causes melanin to be manufactured and built up in keratinocytes, as sun exposure stimulates keratinocytes to secrete chemicals that stimulate melanocytes. The accumulation of melanin in keratinocytes results in the darkening of the skin, or a tan. This increased melanin accumulation protects the DNA of epidermal cells from UV ray damage and the breakdown of folic acid, a nutrient necessary for our health and well-being. In contrast, too much melanin can interfere with the production of vitamin D, an important nutrient involved in calcium absorption. Thus, the amount of melanin present in our skin is dependent on a balance between available sunlight and folic acid destruction, and protection from UV radiation and vitamin D production.

It requires about 10 days after initial sun exposure for melanin synthesis to peak, which is why pale-skinned individuals tend to suffer sunburns of the epidermis initially. Dark-skinned individuals can also get sunburns, but are more protected than are pale-skinned individuals. Melanosomes are temporary structures that are eventually destroyed by fusion with lysosomes; this fact, along with melanin-filled keratinocytes in the stratum corneum sloughing off, makes tanning impermanent.

Too much sun exposure can eventually lead to wrinkling due to the destruction of the cellular structure of the skin, and in severe cases, can cause sufficient DNA damage to result in skin cancer. When there is an irregular accumulation of melanocytes in the skin, freckles appear. Moles are larger masses of melanocytes, and although most are benign, they should be monitored for changes that might indicate the presence of cancer (Figure 5.9).



(a) (b)

FIGURE 5.10 Vitiligo Individuals with vitiligo experience depigmentation that results in lighter colored patches of skin. The condition is especially noticeable on darker skin. (credit: (a) Klaus D. Peter (b) Owl Bridge Media / Wikimedia.)

Other changes in the appearance of skin coloration can be indicative of diseases associated with other body systems. Liver disease or liver cancer can cause the accumulation of bile and the yellow pigment bilirubin, leading to the skin appearing yellow or jaundiced (*jaune* is the French word for "yellow"). Tumors of the pituitary gland can result in the secretion of large amounts of melanocyte-stimulating hormone (MSH), which results in a darkening of the skin. Similarly, Addison's disease can stimulate the release of excess amounts of adrenocorticotropic hormone (ACTH), which can give the skin a deep bronze color. A sudden drop in oxygenation can affect skin color, causing the skin to initially turn ashen (white). With a prolonged reduction in oxygen levels, dark red deoxyhemoglobin becomes dominant in the blood, making the skin appear blue, a condition referred to as cyanosis (*kyanos* is the Greek word for "blue"). This happens when the oxygen supply is restricted, as when someone is experiencing difficulty in breathing because of asthma or a heart attack. However, in these cases the effect on skin color has nothing do with the skin's pigmentation.

INTERACTIVE LINK

This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video (http://openstax.org/l/albino) to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

5.2 Accessory Structures of the Skin

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the accessory structures of the skin
- Describe the structure and function of hair and nails
- Describe the structure and function of sweat glands and sebaceous glands

Accessory structures of the skin include hair, nails, sweat glands, and sebaceous glands. These structures embryologically originate from the epidermis and can extend down through the dermis into the hypodermis.

Hair

Hair is a keratinous filament growing out of the epidermis. It is primarily made of dead, keratinized cells. Strands of hair originate in an epidermal penetration of the dermis called the **hair follicle**. The **hair shaft** is the part of the hair not anchored to the follicle, and much of this is exposed at the skin's surface. The rest of the hair, which is anchored in the follicle, lies below the surface of the skin and is referred to as the **hair root**. The hair root ends deep in the dermis at the **hair bulb**, and includes a layer of mitotically active basal cells called the **hair matrix**. The hair bulb surrounds the **hair papilla**, which is made of connective tissue and contains blood capillaries and nerve endings from the dermis (Figure 5.11).

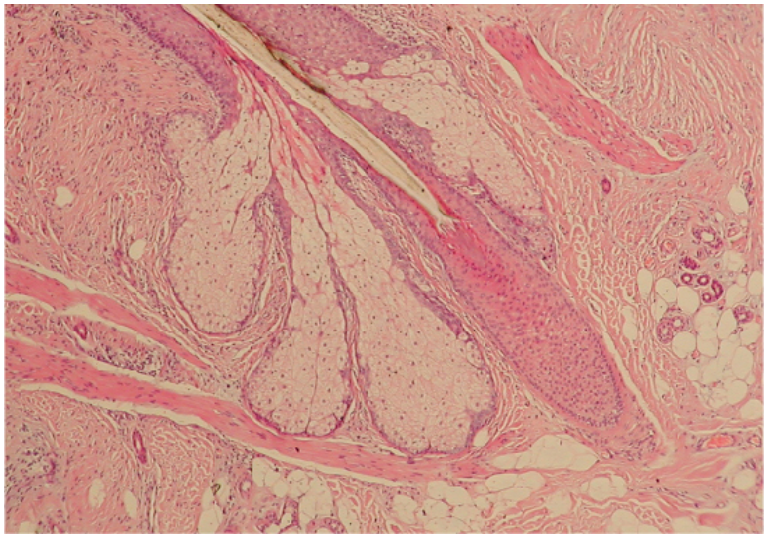


FIGURE 5.12 Hair Follicle The slide shows a cross-section of a hair follicle. Basal cells of the hair matrix in the center differentiate into cells of the inner root sheath. Basal cells at the base of the hair root form the outer root sheath. LM × 4. (credit: modification of work by "kilbad"/Wikimedia Commons)

The wall of the hair follicle is made of three concentric layers of cells. The cells of the **internal root sheath** surround the root of the growing hair and extend just up to the hair shaft. They are derived from the basal cells of the hair matrix. The **external root sheath**, which is an extension of the epidermis, encloses the hair root. It is made of basal cells at the base of the hair root and tends to be more keratinous in the upper regions. The **glassy membrane** is a thick, clear connective tissue sheath covering the hair root, connecting it to the tissue of the dermis.

INTERACTIVE LINK

The hair follicle is made of multiple layers of cells that form from basal cells in the hair matrix and the hair root. Cells of the hair matrix divide and differentiate to form the layers of the hair. Watch this video (http://openstax.org/l/follicle) to learn more about hair follicles.

Hair serves a variety of functions, including protection, sensory input, thermoregulation, and communication. For example, hair on the head protects the skull from the sun. The hair in the nose and ears, and around the eyes (eyelashes) defends the body by trapping and excluding dust particles that may contain allergens and microbes. Hair of the eyebrows prevents sweat and other particles from dripping into and bothering the eyes. Hair also has a sensory function due to sensory innervation by a hair root plexus surrounding the base of each hair follicle. Hair is extremely sensitive to air movement or other disturbances in the environment, much more so than the skin surface. This feature is also useful for the detection of the presence of insects or other potentially damaging substances on the skin surface. Each hair root is connected to a smooth muscle called the **arrector pili** that contracts in response to nerve signals from the sympathetic nervous system, making the external hair shaft "stand up." The primary purpose for this is to trap a layer of air to add insulation. This is visible in humans as goose bumps and even more obvious in animals, such as when a frightened cat raises its fur. Of course, this is much more obvious in organisms with a heavier coat than most humans, such as dogs and cats.

Hair Growth

Hair grows and is eventually shed and replaced by new hair. This occurs in three phases. The first is the **anagen** phase, during which cells divide rapidly at the root of the hair, pushing the hair shaft up and out. The length of this phase is measured in years, typically from 2 to 7 years. The **catagen** phase lasts only 2 to 3 weeks, and marks a transition from the hair follicle's active growth. Finally, during the **telogen** phase, the hair follicle is at rest and no new growth occurs. At the end of this phase, which lasts about 2 to 4 months, another anagen phase begins. The basal cells in the hair matrix then produce a new hair follicle, which pushes the old hair out as the growth cycle repeats itself. Hair typically grows at the rate of 0.3 mm per day during the anagen phase. On average, 50 hairs are lost and replaced per day. Hair loss occurs if there is more hair shed than what is replaced and can happen due to hormonal or dietary changes. Hair loss can also result from the aging process, or the influence of hormones.

exocytosis through a duct without affecting the cells of the gland. There are two types of sweat glands, each secreting slightly different products.

An **eccrine sweat gland** is type of gland that produces a hypotonic sweat for thermoregulation. These glands are found all over the skin's surface, but are especially abundant on the palms of the hand, the soles of the feet, and the forehead (Figure 5.14). They are coiled glands lying deep in the dermis, with the duct rising up to a pore on the skin surface, where the sweat is released. This type of sweat, released by exocytosis, is hypotonic and composed mostly of water, with some salt, antibodies, traces of metabolic waste, and dermicidin, an antimicrobial peptide. Eccrine glands are a primary component of thermoregulation in humans and thus help to maintain homeostasis.

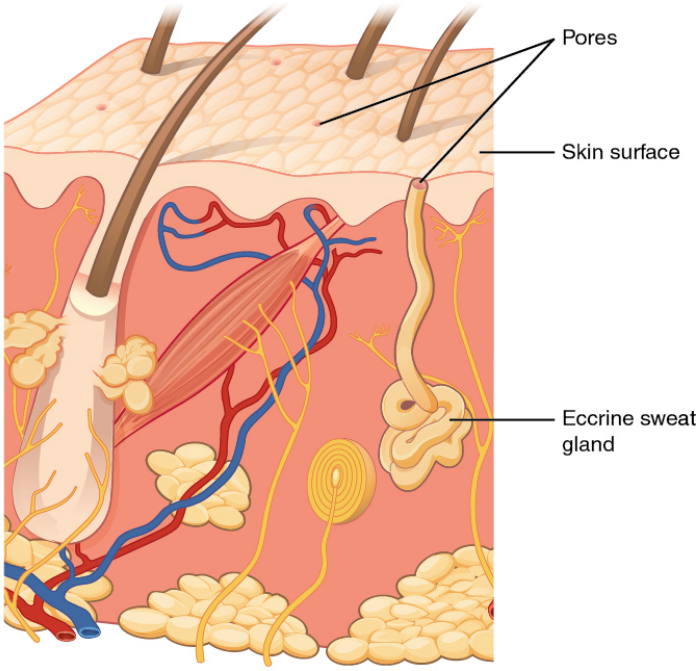


FIGURE 5.14 Eccrine Gland Eccrine glands are coiled glands in the dermis that release sweat that is mostly water.

An **apocrine sweat gland** is usually associated with hair follicles in densely hairy areas, such as armpits and genital regions. Apocrine sweat glands are larger than eccrine sweat glands and lie deeper in the dermis, sometimes even reaching the hypodermis, with the duct normally emptying into the hair follicle. In addition to water and salts, apocrine sweat includes organic compounds that make the sweat thicker and subject to bacterial decomposition and subsequent smell. The release of this sweat is under both nervous and hormonal control, and plays a role in the poorly understood human pheromone response. Most commercial antiperspirants use an aluminum-based compound as their primary active ingredient to stop sweat. When the antiperspirant enters the sweat gland duct, the aluminum-based compounds precipitate due to a change in pH and form a physical block in the duct, which prevents sweat from coming out of the pore.

INTERACTIVE LINK

Sweating regulates body temperature. The composition of the sweat determines whether body odor is a byproduct of sweating. Visit this link (http://openstax.org/l/sweating) to learn more about sweating and body odor.

Sebaceous Glands

A **sebaceous gland** is a type of oil gland that is found all over the body and helps to lubricate and waterproof the skin and hair. Most sebaceous glands are associated with hair follicles. They generate and excrete **sebum**, a mixture of lipids, onto the skin surface, thereby naturally lubricating the dry and dead layer of keratinized cells of the stratum corneum, keeping it pliable. The fatty acids of sebum also have antibacterial properties, and prevent water loss from the skin in low-humidity environments. The secretion of sebum is stimulated by hormones, many of which do not become active until puberty. Thus, sebaceous glands are relatively inactive during childhood.

vibration. Merkel cells, seen scattered in the stratum basale, are also touch receptors. In addition to these specialized receptors, there are sensory nerves connected to each hair follicle, pain and temperature receptors scattered throughout the skin, and motor nerves innervate the arrector pili muscles and glands. This rich innervation helps us sense our environment and react accordingly.

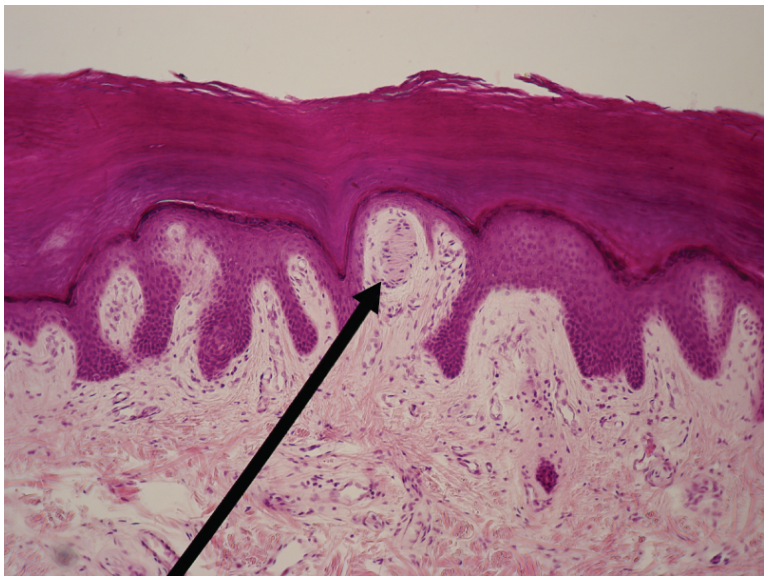


FIGURE 5.15 Light Micrograph of a Meissner Corpuscle In this micrograph of a skin cross-section, you can see a Meissner corpuscle (arrow), a type of touch receptor located in a dermal papilla adjacent to the basement membrane and stratum basale of the overlying epidermis. LM × 100. (credit: "Wbensmith"/Wikimedia Commons)

Thermoregulation

The integumentary system helps regulate body temperature through its tight association with the sympathetic nervous system, the division of the nervous system involved in our fight-or-flight responses. The sympathetic nervous system is continuously monitoring body temperature and initiating appropriate motor responses. Recall that sweat glands, accessory structures to the skin, secrete water, salt, and other substances to cool the body when it becomes warm. Even when the body does not appear to be noticeably sweating, approximately 500 mL of sweat (insensible perspiration) are secreted a day. If the body becomes excessively warm due to high temperatures, vigorous activity (Figure 5.16**ac**), or a combination of the two, sweat glands will be stimulated by the sympathetic nervous system to produce large amounts of sweat, as much as 0.7 to 1.5 L per hour for an active person. When the sweat evaporates from the skin surface, the body is cooled as body heat is dissipated.

In addition to sweating, arterioles in the dermis dilate so that excess heat carried by the blood can dissipate through the skin and into the surrounding environment (Figure 5.16**b**). This accounts for the skin redness that many people experience when exercising.

The accessory structures also have lowered activity, generating thinner hair and nails, and reduced amounts of sebum and sweat. A reduced sweating ability can cause some elderly to be intolerant to extreme heat. Other cells in the skin, such as melanocytes and dendritic cells, also become less active, leading to a paler skin tone and lowered immunity. Wrinkling of the skin occurs due to breakdown of its structure, which results from decreased collagen and elastin production in the dermis, weakening of muscles lying under the skin, and the inability of the skin to retain adequate moisture.

Many anti-aging products can be found in stores today. In general, these products try to rehydrate the skin and thereby fill out the wrinkles, and some stimulate skin growth using hormones and growth factors. Additionally, invasive techniques include collagen injections to plump the tissue and injections of BOTOX® (the name brand of the botulinum neurotoxin) that paralyze the muscles that crease the skin and cause wrinkling.

Vitamin D Synthesis

The epidermal layer of human skin synthesizes **vitamin D** when exposed to UV radiation. In the presence of sunlight, a form of vitamin D_3 called cholecalciferol is synthesized from a derivative of the steroid cholesterol in the skin. The liver converts cholecalciferol to calcidiol, which is then converted to calcitriol (the active chemical form of the vitamin) in the kidneys. Vitamin D is essential for normal absorption of calcium and phosphorous, which are required for healthy bones. The absence of sun exposure can lead to a lack of vitamin D in the body, leading to a condition called **rickets**, a painful condition in children where the bones are misshapen due to a lack of calcium, causing bowleggedness. Elderly individuals who suffer from vitamin D deficiency can develop a condition called osteomalacia, a softening of the bones. In present day society, vitamin D is added as a supplement to many foods, including milk and orange juice, compensating for the need for sun exposure.

In addition to its essential role in bone health, vitamin D is essential for general immunity against bacterial, viral, and fungal infections. Recent studies are also finding a link between insufficient vitamin D and cancer.

5.4 Diseases, Disorders, and Injuries of the Integumentary System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe several different diseases and disorders of the skin
- Describe the effect of injury to the skin and the process of healing

The integumentary system is susceptible to a variety of diseases, disorders, and injuries. These range from annoying but relatively benign bacterial or fungal infections that are categorized as disorders, to skin cancer and severe burns, which can be fatal. In this section, you will learn several of the most common skin conditions.

Diseases

One of the most talked about diseases is skin cancer. Cancer is a broad term that describes diseases caused by abnormal cells in the body dividing uncontrollably. Most cancers are identified by the organ or tissue in which the cancer originates. One common form of cancer is skin cancer. The Skin Cancer Foundation reports that one in five Americans will experience some type of skin cancer in their lifetime. The degradation of the ozone layer in the atmosphere and the resulting increase in exposure to UV radiation has contributed to its rise. Overexposure to UV radiation damages DNA, which can lead to the formation of cancerous lesions. Although melanin offers some protection against DNA damage from the sun, often it is not enough. The fact that cancers can also occur on areas of the body that are normally not exposed to UV radiation suggests that there are additional factors that can lead to cancerous lesions.

In general, cancers result from an accumulation of DNA mutations. These mutations can result in cell populations that do not die when they should and uncontrolled cell proliferation that leads to tumors. Although many tumors are benign (harmless), some produce cells that can mobilize and establish tumors in other organs of the body; this process is referred to as **metastasis**. Cancers are characterized by their ability to metastasize.

Basal Cell Carcinoma

Basal cell carcinoma is a form of cancer that affects the mitotically active stem cells in the stratum basale of the

(credit: the National Cancer Institute / Centers for Disease Control)

Doctors often give their patients the following ABCDE mnemonic to help with the diagnosis of early-stage melanoma. If you observe a mole on your body displaying these signs, consult a doctor.

- **A**symmetry – the two sides are not symmetrical
- **B**orders – the edges are irregular in shape
- **C**olor – the color is varied shades of brown or black
- **D**iameter – it is larger than 6 mm (0.24 in)
- **E**volving – its shape has changed

Some specialists cite the following additional signs for the most serious form, nodular melanoma:

- **E**levated – it is raised on the skin surface
- **F**irm – it feels hard to the touch
- **G**rowing – it is getting larger

Skin Disorders

Two common skin disorders are eczema and acne. Eczema is an inflammatory condition and occurs in individuals of all ages. Acne involves the clogging of pores, which can lead to infection and inflammation, and is often seen in adolescents. Other disorders, not discussed here, include seborrheic dermatitis (on the scalp), psoriasis, cold sores, impetigo, scabies, hives, and warts.

Eczema

Eczema is an allergic reaction that manifests as dry, itchy patches of skin that resemble rashes (Figure 5.21). It may be accompanied by swelling of the skin, flaking, and in severe cases, bleeding. Many who suffer from eczema have antibodies against dust mites in their blood, but the link between eczema and allergy to dust mites has not been proven. Symptoms are usually managed with moisturizers, corticosteroid creams, and immunosuppressants.



FIGURE 5.21 Eczema Eczema is a common skin disorder that presents as a red, flaky rash. (credit: "Jambula" Wikimedia Commons / NIAID, Flickr)

Acne

Acne is a skin disturbance that typically occurs on areas of the skin that are rich in sebaceous glands (face and back). It is most common along with the onset of puberty due to associated hormonal changes, but can also occur in infants and continue into adulthood. Hormones, such as androgens, stimulate the release of sebum. An overproduction and accumulation of sebum along with keratin can block hair follicles. This plug is initially white. The sebum, when oxidized by exposure to air, turns black. Acne results from infection by acne-causing bacteria (*Propionibacterium* and *Staphylococcus*), which can lead to redness and potential scarring due to the natural wound healing process (Figure 5.22).

stem cells of the stratum basale can recreate the epidermis, fibroblasts mobilize and divide rapidly to repair the damaged tissue by collagen deposition, forming granulation tissue. Blood capillaries follow the fibroblasts and help increase blood circulation and oxygen supply to the area. Immune cells, such as macrophages, roam the area and engulf any foreign matter to reduce the chance of infection.

Burns

A burn results when the skin is damaged by intense heat, radiation, electricity, or chemicals. The damage results in the death of skin cells, which can lead to a massive loss of fluid. Dehydration, electrolyte imbalance, and renal and circulatory failure follow, which can be fatal. Burn patients are treated with intravenous fluids to offset dehydration, as well as intravenous nutrients that enable the body to repair tissues and replace lost proteins. Another serious threat to the lives of burn patients is infection. Burned skin is extremely susceptible to bacteria and other pathogens, due to the loss of protection by intact layers of skin.

Burns are sometimes measured in terms of the size of the total surface area affected. This is referred to as the "rule of nines," which associates specific anatomical areas with a percentage that is a factor of nine (Figure 5.23). Burns are also classified by the degree of their severity. A **first-degree burn** is a superficial burn that affects only the epidermis. Although the skin may be painful and swollen, these burns typically heal on their own within a few days. Mild sunburn fits into the category of a first-degree burn. A **second-degree burn** goes deeper and affects both the epidermis and a portion of the dermis. These burns result in swelling and a painful blistering of the skin. It is important to keep the burn site clean and sterile to prevent infection. If this is done, the burn will heal within several weeks. A **third-degree burn** fully extends into the epidermis and dermis, destroying the tissue and affecting the nerve endings and sensory function. These are serious burns that may appear white, red, or black; they require medical attention and will heal slowly without it. A **fourth-degree burn** is even more severe, affecting the underlying muscle and bone. Oddly, third and fourth-degree burns are usually not as painful because the nerve endings themselves are damaged. Full-thickness burns cannot be repaired by the body, because the local tissues used for repair are damaged and require excision (debridement), or amputation in severe cases, followed by grafting of the skin from an unaffected part of the body, or from skin grown in tissue culture for grafting purposes.

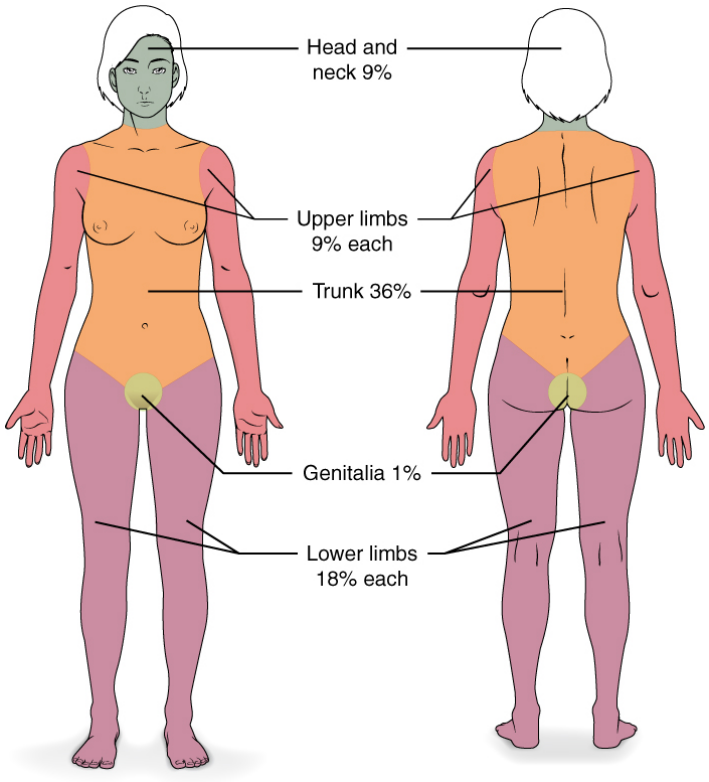


FIGURE 5.23 Calculating the Size of a Burn The size of a burn will guide decisions made about the need for specialized treatment. Specific parts of the body are associated with a percentage of body area.

Key Terms

acne skin condition due to infected sebaceous glands
albinism genetic disorder that affects the skin, in which there is no melanin production
anagen active phase of the hair growth cycle
apocrine sweat gland type of sweat gland that is associated with hair follicles in the armpits and genital regions
arrector pili smooth muscle that is activated in response to external stimuli that pull on hair follicles and make the hair "stand up"
basal cell type of stem cell found in the stratum basale and in the hair matrix that continually undergoes cell division, producing the keratinocytes of the epidermis
basal cell carcinoma cancer that originates from basal cells in the epidermis of the skin
bedsore sore on the skin that develops when regions of the body start necrotizing due to constant pressure and lack of blood supply; also called decubitis ulcers
callus thickened area of skin that arises due to constant abrasion
catagen transitional phase marking the end of the anagen phase of the hair growth cycle
corn type of callus that is named for its shape and the elliptical motion of the abrasive force
cortex in hair, the second or middle layer of keratinocytes originating from the hair matrix, as seen in a cross-section of the hair bulb
cuticle in hair, the outermost layer of keratinocytes originating from the hair matrix, as seen in a cross-section of the hair bulb
dermal papilla (plural = dermal papillae) extension of the papillary layer of the dermis that increases surface contact between the epidermis and dermis
dermis layer of skin between the epidermis and hypodermis, composed mainly of connective tissue and containing blood vessels, hair follicles, sweat glands, and other structures
desmosome structure that forms an impermeable junction between cells
eccrine sweat gland type of sweat gland that is common throughout the skin surface; it produces a hypotonic sweat for thermoregulation
eczema skin condition due to an allergic reaction, which resembles a rash
elastin fibers fibers made of the protein elastin that increase the elasticity of the dermis
eleiden clear protein-bound lipid found in the stratum lucidum that is derived from keratohyalin and helps to prevent water loss
epidermis outermost tissue layer of the skin
eponychium nail fold that meets the proximal end of the nail body, also called the cuticle
external root sheath outer layer of the hair follicle that is an extension of the epidermis, which encloses the hair root
first-degree burn superficial burn that injures only the epidermis
fourth-degree burn burn in which full thickness of the skin and underlying muscle and bone is damaged
glassy membrane layer of connective tissue that surrounds the base of the hair follicle, connecting it to the dermis
hair keratinous filament growing out of the epidermis
hair bulb structure at the base of the hair root that surrounds the dermal papilla
hair follicle cavity or sac from which hair originates
hair matrix layer of basal cells from which a strand of hair grows
hair papilla mass of connective tissue, blood capillaries, and nerve endings at the base of the hair follicle
hair root part of hair that is below the epidermis anchored to the follicle
hair shaft part of hair that is above the epidermis but is not anchored to the follicle
hypodermis connective tissue connecting the integument to the underlying bone and muscle
hyponychium thickened layer of stratum corneum that lies below the free edge of the nail
integumentary system skin and its accessory structures
internal root sheath innermost layer of keratinocytes in the hair follicle that surround the hair root up to the hair shaft
keloid type of scar that has layers raised above the skin surface
keratin type of structural protein that gives skin, hair, and nails its hard, water-resistant properties
keratinocyte cell that produces keratin and is the most predominant type of cell found in the epidermis
keratohyalin granulated protein found in the stratum granulosum
Langerhans cell specialized dendritic cell found in the stratum spinosum that functions as a macrophage
lunula basal part of the nail body that consists of a crescent-shaped layer of thick epithelium
medulla in hair, the innermost layer of keratinocytes originating from the hair matrix
Meissner corpuscle (also, tactile corpuscle) receptor

dead keratinized cells, and gets its color from melanin pigments. Nails, also made of dead keratinized cells, protect the extremities of our fingers and toes from mechanical damage. Sweat glands and sebaceous glands produce sweat and sebum, respectively. Each of these fluids has a role to play in maintaining homeostasis. Sweat cools the body surface when it gets overheated and helps excrete small amounts of metabolic waste. Sebum acts as a natural moisturizer and keeps the dead, flaky, outer keratin layer healthy.

5.3 Functions of the Integumentary System

The skin plays important roles in protection, sensing stimuli, thermoregulation, and vitamin D synthesis. It is the first layer of defense to prevent dehydration, infection, and injury to the rest of the body. Sweat glands in the skin allow the skin surface to cool when the body gets overheated. Thermoregulation is also accomplished by the dilation or constriction of heat-carrying blood vessels in the skin. Immune cells present among the skin layers patrol the areas to keep them free of foreign materials. Fat stores in the hypodermis aid in both thermoregulation and protection. Finally, the skin plays a role in the synthesis of vitamin D, which is necessary for our well-being but not easily available in natural foods.

5.4 Diseases, Disorders, and Injuries of the Integumentary System

Skin cancer is a result of damage to the DNA of skin cells, often due to excessive exposure to UV radiation. Basal cell carcinoma and squamous cell carcinoma are highly curable, and arise from cells in the stratum basale and stratum spinosum, respectively. Melanoma is the most dangerous form of skin cancer, affecting melanocytes, which can spread/metastasize to other organs. Burns are an injury to the skin that occur as a result of exposure to extreme heat, radiation, or chemicals. First-degree and second-degree burns usually heal quickly, but third-degree burns can be fatal because they penetrate the full thickness of the skin. Scars occur when there is repair of skin damage. Fibroblasts generate scar tissue in the form of collagen, which forms a basket-weave pattern that looks different from normal skin.

Bedsores and stretch marks are the result of excessive pressure on the skin and underlying tissue. Bedsores are characterized by necrosis of tissue due to immobility, whereas stretch marks result from rapid growth. Eczema is an allergic reaction that manifests as a rash, and acne results from clogged sebaceous glands. Eczema and acne are usually long-term skin conditions that may be treated successfully in mild cases. Calluses and corns are the result of abrasive pressure on the skin.

Interactive Link Questions

1. The skin consists of two layers and a closely associated layer. View this animation (http://openstax.org/l/layers) to learn more about layers of the skin. What are the basic functions of each of these layers?
2. Figure 5.4 If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?
3. Figure 5.6 If you zoom on the cells of the stratum spinosum, what is distinctive about them?
4. This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video (http://openstax.org/l/albino) to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

Review Questions

5. The papillary layer of the dermis is most closely associated with which layer of the epidermis?
   a. stratum spinosum
   b. stratum corneum
   c. stratum granulosum
   d. stratum basale
6. Langerhans cells are commonly found in the _____.
   a. stratum spinosum
   b. stratum corneum
   c. stratum granulosum
   d. stratum basale

22. An individual has spent too much time sun bathing. Not only is their skin painful to touch, but small blisters have appeared in the affected area. This indicates that they have damaged which layers of skin?
   a. epidermis only
   b. hypodermis only
   c. epidermis and hypodermis
   d. epidermis and dermis

23. After a skin injury, the body initiates a wound-healing response. The first step of this response is the formation of a blood clot to stop bleeding. Which of the following would be the next response?
   a. increased production of melanin by melanocytes
   b. increased production of connective tissue
   c. an increase in Pacinian corpuscles around the wound
   d. an increased activity in the stratum lucidum

24. Squamous cell carcinomas are the second most common of the skin cancers and are capable of metastasizing if not treated. This cancer affects which cells?
   a. basal cells of the stratum basale
   b. melanocytes of the stratum basale
   c. keratinocytes of the stratum spinosum
   d. Langerhans cells of the stratum lucidum

Critical Thinking Questions

25. What determines the color of skin, and what is the process that darkens skin when it is exposed to UV light?

26. Cells of the epidermis derive from stem cells of the stratum basale. Describe how the cells change as they become integrated into the different layers of the epidermis.

27. Explain the differences between eccrine and apocrine sweat glands.

28. Describe the structure and composition of nails.

29. Why do people sweat excessively when exercising outside on a hot day?

30. Explain your skin's response to a drop in body core temperature.

31. Why do teenagers often experience acne?

32. Why do scars look different from surrounding skin?

- supports the body
- facilitates movement
- protects internal organs
- produces blood cells
- stores and releases minerals and fat

Support, Movement, and Protection

The most apparent functions of the skeletal system are the gross functions—those visible by observation. Simply by looking at a person, you can see how the bones support, facilitate movement, and protect the human body.

Just as the steel beams of a building provide a scaffold to support its weight, the bones and cartilage of your skeletal system compose the scaffold that supports the rest of your body. Without the skeletal system, you would be a limp mass of organs, muscle, and skin.

Bones also facilitate movement by serving as points of attachment for your muscles. While some bones only serve as a support for the muscles, others also transmit the forces produced when your muscles contract. From a mechanical point of view, bones act as levers and joints serve as fulcrums (Figure 6.2). Unless a muscle spans a joint and contracts, a bone is not going to move. For information on the interaction of the skeletal and muscular systems, that is, the musculoskeletal system, seek additional content.



FIGURE 6.2 Bones Support Movement Bones act as levers when muscles span a joint and contract. (credit: Benjamin J. DeLong)

Bones also protect internal organs from injury by covering or surrounding them. For example, your ribs protect your lungs and heart, the bones of your vertebral column (spine) protect your spinal cord, and the bones of your cranium (skull) protect your brain (Figure 6.3).

the spine. Lateral curvatures (scoliosis) can be severe enough to slip under the shoulder blade (scapula) forcing it up as a hump. Spinal curvatures can also be excessive dorsoventrally (kyphosis) causing a hunch back and thoracic compression. These curvatures often appear in preteens as the result of poor posture, abnormal growth, or indeterminate causes. Mostly, they are readily treated by orthopedists. As people age, accumulated spinal column injuries and diseases like osteoporosis can also lead to curvatures of the spine, hence the stooping you sometimes see in the elderly.

Some orthopedists sub-specialize in sports medicine, which addresses both simple injuries, such as a sprained ankle, and complex injuries, such as a torn rotator cuff in the shoulder. Treatment can range from exercise to surgery.

Mineral Storage, Energy Storage, and Hematopoiesis

On a metabolic level, bone tissue performs several critical functions. For one, the bone matrix acts as a reservoir for a number of minerals important to the functioning of the body, especially calcium, and phosphorus. These minerals, incorporated into bone tissue, can be released back into the bloodstream to maintain levels needed to support physiological processes. Calcium ions, for example, are essential for muscle contractions and controlling the flow of other ions involved in the transmission of nerve impulses.

Bone also serves as a site for fat storage and blood cell production. The softer connective tissue that fills the interior of most bone is referred to as bone marrow (Figure 6.5). There are two types of bone marrow: yellow marrow and red marrow. **Yellow marrow** contains adipose tissue; the triglycerides stored in the adipocytes of the tissue can serve as a source of energy. **Red marrow** is where **hematopoiesis**—the production of blood cells—takes place. Red blood cells, white blood cells, and platelets are all produced in the red marrow.

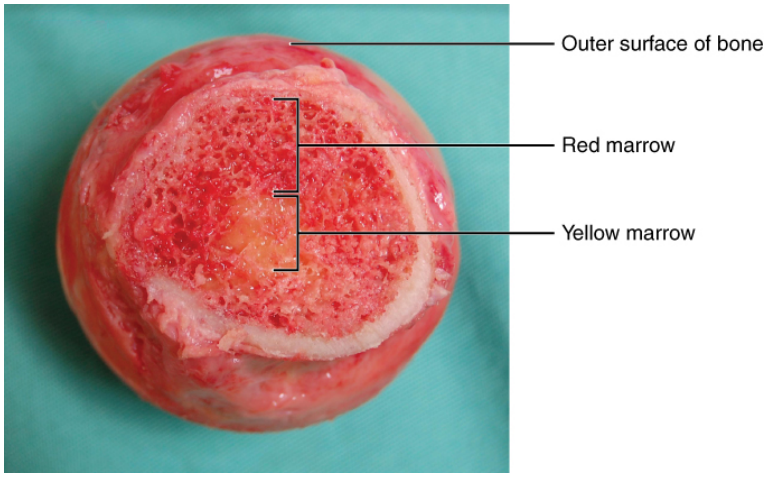


FIGURE 6.5 Head of Femur Showing Red and Yellow Marrow The head of the femur contains both yellow and red marrow. Yellow marrow stores fat. Red marrow is responsible for hematopoiesis. (credit: modification of work by "stevenfruitsmaak"/Wikimedia Commons)

6.2 Bone Classification

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Classify bones according to their shapes
- Describe the function of each category of bones

The 206 bones that compose the adult skeleton are divided into five categories based on their shapes (Figure 6.6). Their shapes and their functions are related such that each categorical shape of bone has a distinct function.

Flat Bones

The term "**flat bone**" is somewhat of a misnomer because, although a flat bone is typically thin, it is also often curved. Examples include the cranial (skull) bones, the scapulae (shoulder blades), the sternum (breastbone), and the ribs. Flat bones serve as points of attachment for muscles and often protect internal organs.

Irregular Bones

An **irregular bone** is one that does not have any easily characterized shape and therefore does not fit any other classification. These bones tend to have more complex shapes, like the vertebrae that support the spinal cord and protect it from compressive forces. Many facial bones, particularly the ones containing sinuses, are classified as irregular bones.

Sesamoid Bones

A **sesamoid bone** is a small, round bone that, as the name suggests, is shaped like a sesame seed. These bones form in tendons (the sheaths of tissue that connect bones to muscles) where a great deal of pressure is generated in a joint. The sesamoid bones protect tendons by helping them overcome compressive forces. Sesamoid bones vary in number and placement from person to person but are typically found in tendons associated with the feet, hands, and knees. The patellae (singular = patella) are the only sesamoid bones found in common with every person. Table 6.1 reviews bone classifications with their associated features, functions, and examples.

Bone Classifications

Bone classification	Features	Function(s)	Examples
Long	Cylinder-like shape, longer than it is wide	Leverage	Femur, tibia, fibula, metatarsals, humerus, ulna, radius, metacarpals, phalanges
Short	Cube-like shape, approximately equal in length, width, and thickness	Provide stability, support, while allowing for some motion	Carpals, tarsals
Flat	Thin and curved	Points of attachment for muscles; protectors of internal organs	Sternum, ribs, scapulae, cranial bones
Irregular	Complex shape	Protect internal organs	Vertebrae, facial bones
Sesamoid	Small and round; embedded in tendons	Protect tendons from compressive forces	Patellae

TABLE 6.1

6.3 Bone Structure

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the anatomical features of a bone
- Define and list examples of bone markings
- Describe the histology of bone tissue
- Compare and contrast compact and spongy bone
- Identify the structures that compose compact and spongy bone
- Describe how bones are nourished and innervated

periosteum covers the entire outer surface except where the epiphyses meet other bones to form joints (Figure 6.8). In this region, the epiphyses are covered with **articular cartilage**, a thin layer of cartilage that reduces friction and acts as a shock absorber.

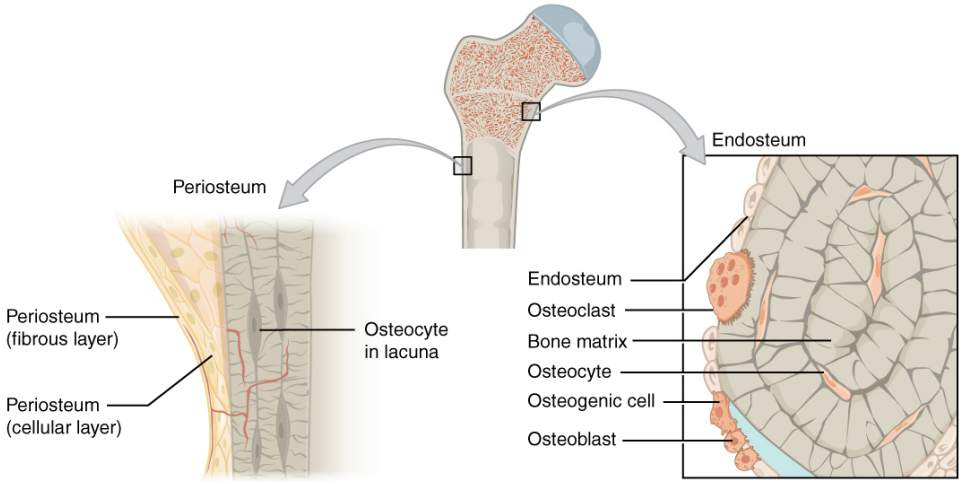


FIGURE 6.8 Periosteum and Endosteum The periosteum forms the outer surface of bone, and the endosteum lines the medullary cavity.

Flat bones, like those of the cranium, consist of a layer of **diploë** (spongy bone), lined on either side by a layer of compact bone (Figure 6.9). The two layers of compact bone and the interior spongy bone work together to protect the internal organs. If the outer layer of a cranial bone fractures, the brain is still protected by the intact inner layer.

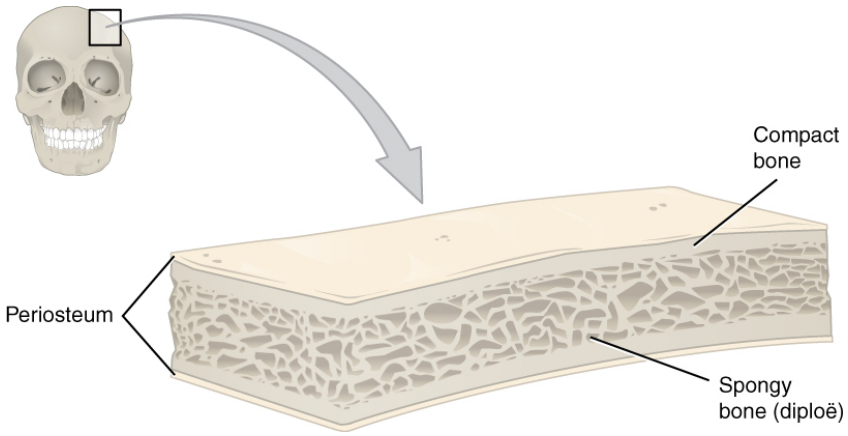


FIGURE 6.9 Anatomy of a Flat Bone This cross-section of a flat bone shows the spongy bone (diploë) lined on either side by a layer of compact bone.

Bone Markings

The surface features of bones vary considerably, depending on the function and location in the body. Table 6.2 describes the bone markings, which are illustrated in (Figure 6.10). There are three general classes of bone markings: (1) articulations, (2) projections, and (3) holes. As the name implies, an **articulation** is where two bone surfaces come together (articulus = "joint"). These surfaces tend to conform to one another, such as one being rounded and the other cupped, to facilitate the function of the articulation. A **projection** is an area of a bone that projects above the surface of the bone. These are the attachment points for tendons and ligaments. In general, their size and shape is an indication of the forces exerted through the attachment to the bone. A **hole** is an opening or groove in the bone that allows blood vessels and nerves to enter the bone. As with the other markings, their size and shape reflect the size of the vessels and nerves that penetrate the bone at these points.

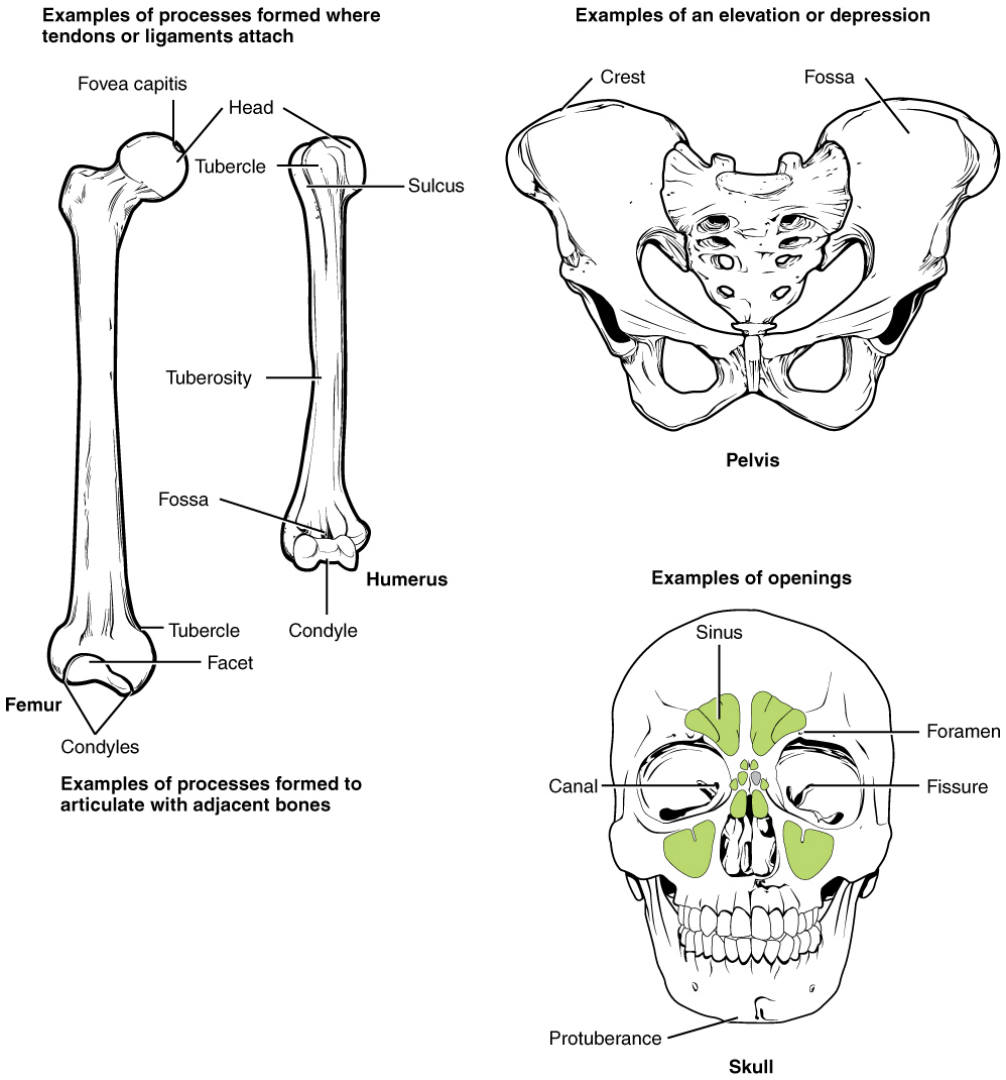


FIGURE 6.10 Bone Features The surface features of bones depend on their function, location, attachment of ligaments and tendons, or the penetration of blood vessels and nerves.

Bone Cells and Tissue

Bone contains a relatively small number of cells entrenched in a matrix of collagen fibers that provide a surface for inorganic salt crystals to adhere. These salt crystals form when calcium phosphate and calcium carbonate combine to create hydroxyapatite, which incorporates other inorganic salts like magnesium hydroxide, fluoride, and sulfate as it crystallizes, or calcifies, on the collagen fibers. The hydroxyapatite crystals give bones their hardness and strength, while the collagen fibers give them flexibility so that they are not brittle.

Although bone cells compose a small amount of the bone volume, they are crucial to the function of bones. Four types of cells are found within bone tissue: osteoblasts, osteocytes, osteogenic cells, and osteoclasts (Figure 6.11).

Cell type	Function	Location
Osteocytes	Maintain mineral concentration of matrix	Entrapped in matrix
Osteoclasts	Bone resorption	Bone surfaces and at sites of old, injured, or unneeded bone

TABLE 6.3

Compact and Spongy Bone

The differences between compact and spongy bone are best explored via their histology. Most bones contain compact and spongy osseous tissue, but their distribution and concentration vary based on the bone's overall function. Compact bone is dense so that it can withstand compressive forces, while spongy (cancellous) bone has open spaces and supports shifts in weight distribution.

Compact Bone

Compact bone is the denser, stronger of the two types of bone tissue (Figure 6.12). It can be found under the periosteum and in the diaphyses of long bones, where it provides support and protection.

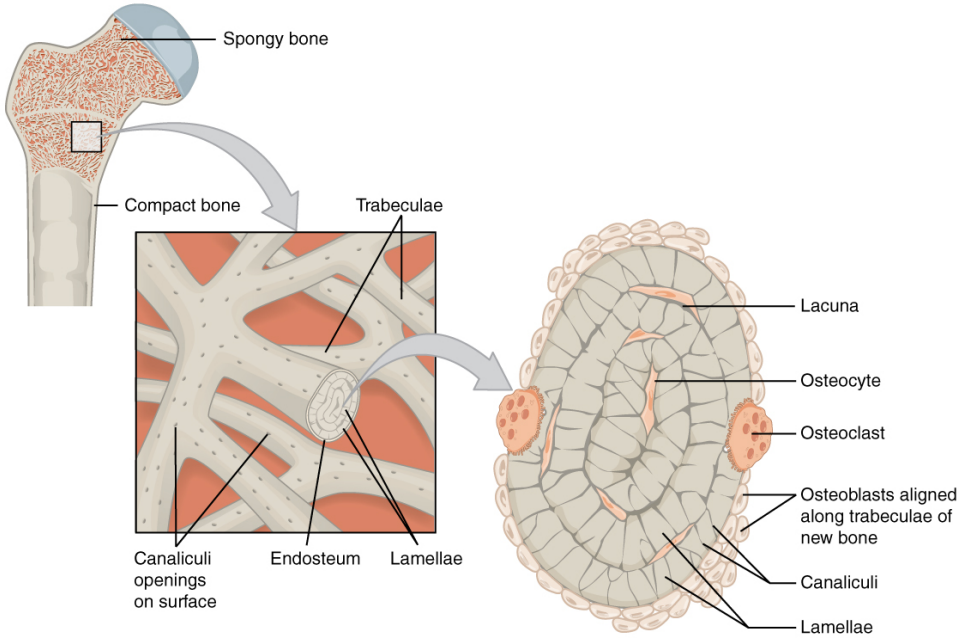


FIGURE 6.13 Diagram of Spongy Bone Spongy bone is composed of trabeculae that contain the osteocytes. Red marrow fills the spaces in some bones.

Aging and the...

Skeletal System: Paget's Disease

Paget's disease usually occurs in adults over age 40. It is a disorder of the bone remodeling process that begins with overactive osteoclasts. This means more bone is resorbed than is laid down. The osteoblasts try to compensate but the new bone they lay down is weak and brittle and therefore prone to fracture.

While some people with Paget's disease have no symptoms, others experience pain, bone fractures, and bone deformities (Figure 6.14). Bones of the pelvis, skull, spine, and legs are the most commonly affected. When occurring in the skull, Paget's disease can cause headaches and hearing loss.

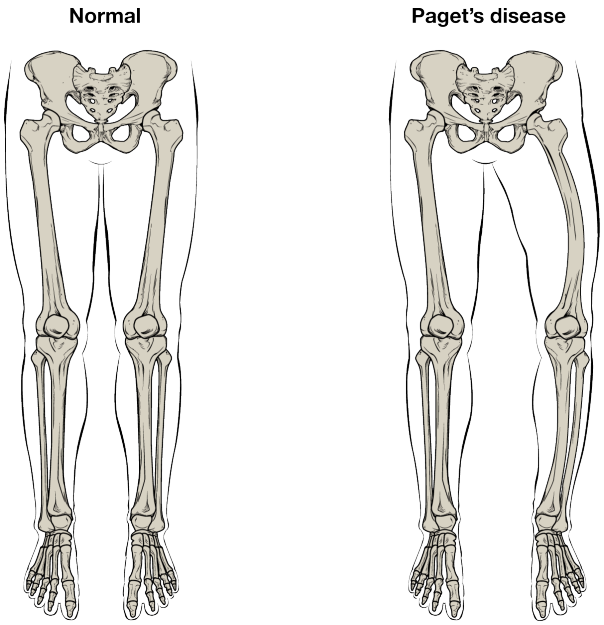


FIGURE 6.14 Paget's Disease Normal leg bones are relatively straight, but those affected by Paget's disease are porous and curved.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/microbone) to see the microscopic features of a bone.

6.4 Bone Formation and Development

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the function of cartilage
- List the steps of intramembranous ossification
- List the steps of endochondral ossification
- Explain the growth activity at the epiphyseal plate
- Compare and contrast the processes of modeling and remodeling

In the early stages of embryonic development, the embryo's skeleton consists of fibrous membranes and hyaline cartilage. By the sixth or seventh week of embryonic life, the actual process of bone development, **ossification** (osteogenesis), begins. There are two osteogenic pathways—intramembranous ossification and endochondral ossification—but bone is the same regardless of the pathway that produces it.

Cartilage Templates

Bone is a replacement tissue; that is, it uses a model tissue on which to lay down its mineral matrix. For skeletal development, the most common template is cartilage. During fetal development, a framework is laid down that determines where bones will form. This framework is a flexible, semi-solid matrix produced by chondroblasts and consists of hyaluronic acid, chondroitin sulfate, collagen fibers, and water. As the matrix surrounds and isolates chondroblasts, they are called chondrocytes. Unlike most connective tissues, cartilage is avascular, meaning that it has no blood vessels supplying nutrients and removing metabolic wastes. All of these functions are carried on by diffusion through the matrix. This is why damaged cartilage does not repair itself as readily as most tissues do.

Throughout fetal development and into childhood growth and development, bone forms on the cartilaginous matrix. By the time a fetus is born, most of the cartilage has been replaced with bone. Some additional cartilage will be replaced throughout childhood, and some cartilage remains in the adult skeleton.

Intramembranous Ossification

During **intramembranous ossification**, compact and spongy bone develops directly from sheets of mesenchymal (undifferentiated) connective tissue. The flat bones of the face, most of the cranial bones, and the clavicles (collarbones) are formed via intramembranous ossification.

The process begins when mesenchymal cells in the embryonic skeleton gather together and begin to differentiate into specialized cells (Figure 6.16**a**). Some of these cells will differentiate into capillaries, while others will become osteogenic cells and then osteoblasts. Although they will ultimately be spread out by the formation of bone tissue, early osteoblasts appear in a cluster called an **ossification center**.

The osteoblasts secrete **osteoid**, uncalcified matrix, which calcifies (hardens) within a few days as mineral salts are deposited on it, thereby entrapping the osteoblasts within. Once entrapped, the osteoblasts become osteocytes (Figure 6.16**b**). As osteoblasts transform into osteocytes, osteogenic cells in the surrounding connective tissue differentiate into new osteoblasts.

Osteoid (unmineralized bone matrix) secreted around the capillaries results in a trabecular matrix, while osteoblasts on the surface of the spongy bone become the periosteum (Figure 6.16**c**). The periosteum then creates a protective layer of compact bone superficial to the trabecular bone. The trabecular bone crowds nearby blood vessels, which eventually condense into red marrow (Figure 6.16**d**).

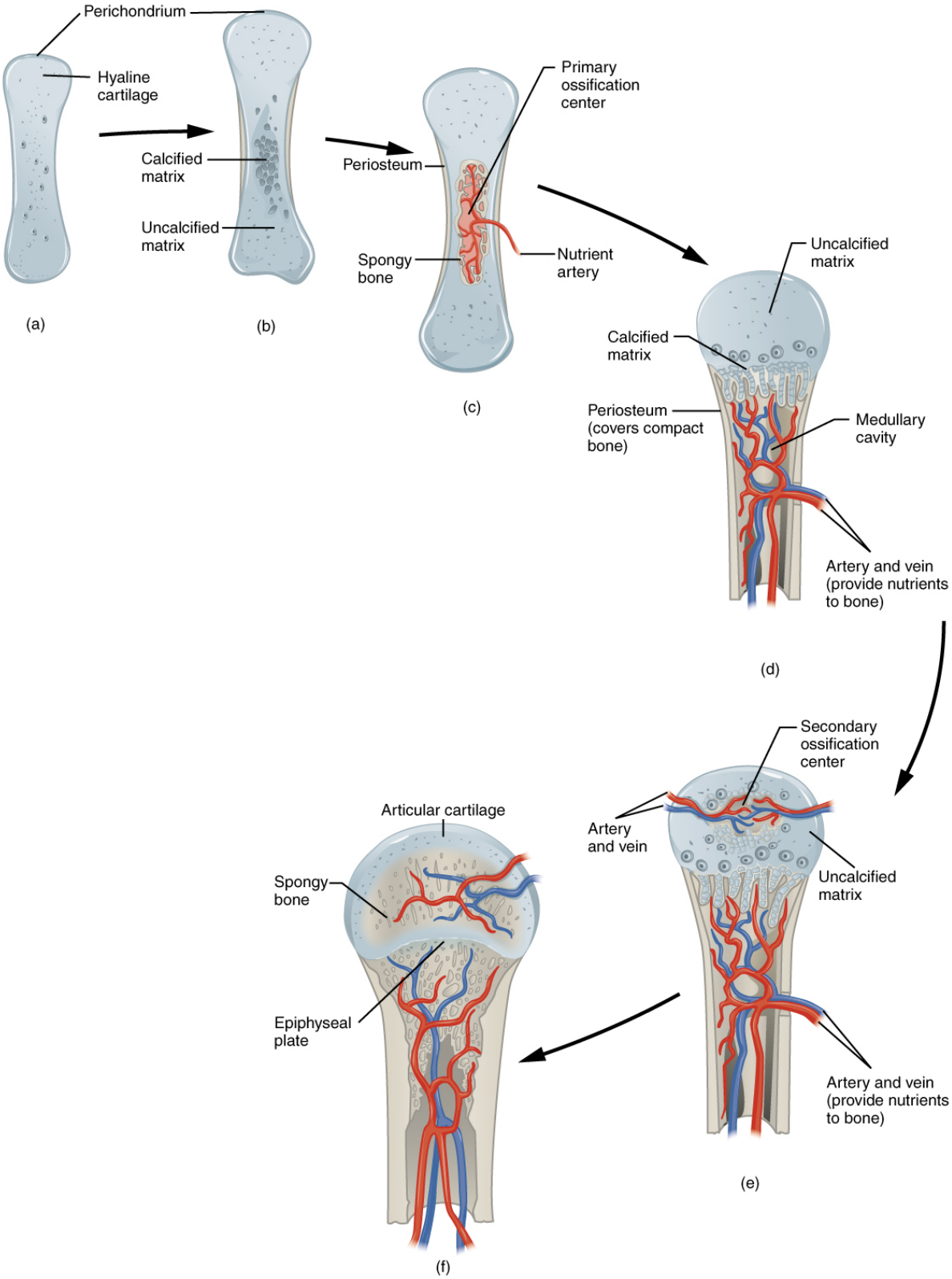


FIGURE 6.17 Endochondral Ossification Endochondral ossification follows five steps. (a) Mesenchymal cells differentiate into chondrocytes. (b) The cartilage model of the future bony skeleton and the perichondrium form. (c) Capillaries penetrate cartilage. Perichondrium transforms into periosteum. Periosteal collar develops. Primary ossification center develops. (d) Cartilage and chondrocytes continue to grow at ends of the bone. (e) Secondary ossification centers develop. (f) Cartilage remains at epiphyseal (growth) plate and at joint surface as articular cartilage.

As more matrix is produced, the chondrocytes in the center of the cartilaginous model grow in size. As the matrix

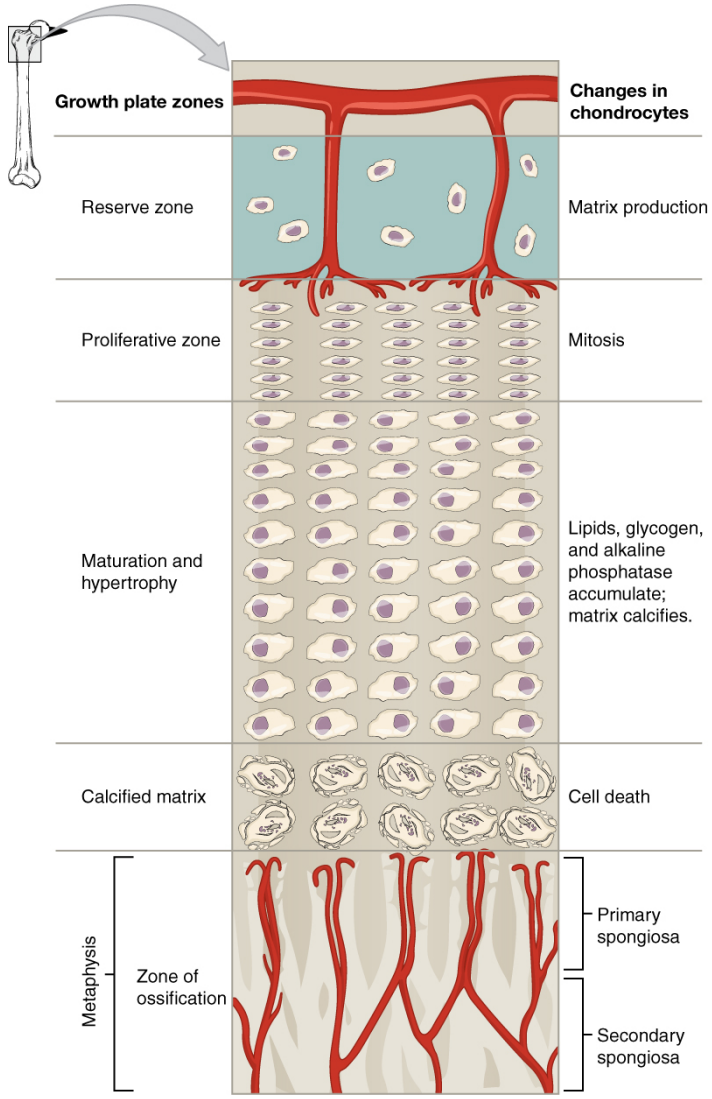


FIGURE 6.18 Longitudinal Bone Growth The epiphyseal plate is responsible for longitudinal bone growth.

The **proliferative zone** is the next layer toward the diaphysis and contains stacks of slightly larger chondrocytes. It makes new chondrocytes (via mitosis) to replace those that die at the diaphyseal end of the plate. Chondrocytes in the next layer, the **zone of maturation and hypertrophy**, are older and larger than those in the proliferative zone. The more mature cells are situated closer to the diaphyseal end of the plate. The longitudinal growth of bone is a result of cellular division in the proliferative zone and the maturation of cells in the zone of maturation and hypertrophy.

Most of the chondrocytes in the **zone of calcified matrix**, the zone closest to the diaphysis, are dead because the matrix around them has calcified. Capillaries and osteoblasts from the diaphysis penetrate this zone, and the osteoblasts secrete bone tissue on the remaining calcified cartilage. Thus, the zone of calcified matrix connects the epiphyseal plate to the diaphysis. A bone grows in length when osseous tissue is added to the diaphysis.

Bones continue to grow in length until early adulthood. The rate of growth is controlled by hormones, which will be discussed later. When the chondrocytes in the epiphyseal plate cease their proliferation and bone replaces the cartilage, longitudinal growth stops. All that remains of the epiphyseal plate is the **epiphyseal line** (Figure 6.19).

like swimming, in which the body is less likely to experience collisions or compressive forces, are recommended. Braces to support legs, ankles, knees, and wrists are used as needed. Canes, walkers, or wheelchairs can also help compensate for weaknesses.

When bones do break, casts, splints, or wraps are used. In some cases, metal rods may be surgically implanted into the long bones of the arms and legs. Research is currently being conducted on using bisphosphonates to treat OI. Smoking and being overweight are especially risky in people with OI, since smoking is known to weaken bones, and extra body weight puts additional stress on the bones.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/bonegrows) to see how a bone grows.

6.5 Fractures: Bone Repair

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Differentiate among the different types of fractures
- Describe the steps involved in bone repair

A **fracture** is a broken bone. It will heal whether or not a physician resets it in its anatomical position. If the bone is not reset correctly, the healing process will keep the bone in its deformed position.

When a broken bone is manipulated and set into its natural position without surgery, the procedure is called a **closed reduction**. **Open reduction** requires surgery to expose the fracture and reset the bone. While some fractures can be minor, others are quite severe and result in grave complications. For example, a fractured diaphysis of the femur has the potential to release fat globules into the bloodstream. These can become lodged in the capillary beds of the lungs, leading to respiratory distress and if not treated quickly, death.

Types of Fractures

Fractures are classified by their complexity, location, and other features (Figure 6.20). Table 6.4 outlines common types of fractures. Some fractures may be described using more than one term because it may have the features of more than one type (e.g., an open transverse fracture).

Types of Fractures

Type of fracture	Description
Transverse	Occurs straight across the long axis of the bone
Oblique	Occurs at an angle that is not 90 degrees
Spiral	Bone segments are pulled apart as a result of a twisting motion
Comminuted	Several breaks result in many small pieces between two large segments
Impacted	One fragment is driven into the other, usually as a result of compression
Greenstick	A partial fracture in which only one side of the bone is broken
Open (or compound)	A fracture in which at least one end of the broken bone tears through the skin; carries a high risk of infection
Closed (or simple)	A fracture in which the skin remains intact

TABLE 6.4

Bone Repair

When a bone breaks, blood flows from any vessel torn by the fracture. These vessels could be in the periosteum, osteons, and/or medullary cavity. The blood begins to clot, and about six to eight hours after the fracture, the clotting blood has formed a **fracture hematoma** (Figure 6.21**a**). The disruption of blood flow to the bone results in the death of bone cells around the fracture.

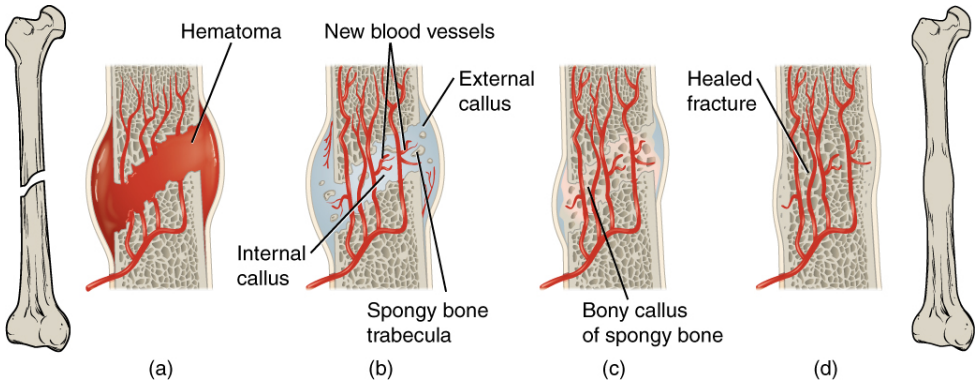


FIGURE 6.21 **Stages in Fracture Repair** The healing of a bone fracture follows a series of progressive steps: (a) A fracture hematoma forms. (b) Internal and external calli form. (c) Cartilage of the calli is replaced by trabecular bone. (d) Remodeling occurs.

Within about 48 hours after the fracture, chondrocytes from the endosteum have created an **internal callus** (plural = calli) by secreting a fibrocartilaginous matrix between the two ends of the broken bone, while the periosteal chondrocytes and osteoblasts create an **external callus** of hyaline cartilage and bone, respectively, around the outside of the break (Figure 6.21**b**). This stabilizes the fracture.

Over the next several weeks, osteoclasts resorb the dead bone; osteogenic cells become active, divide, and differentiate into osteoblasts. The cartilage in the calli is replaced by trabecular bone via endochondral ossification (Figure 6.21**c**).

Eventually, the internal and external calli unite, compact bone replaces spongy bone at the outer margins of the

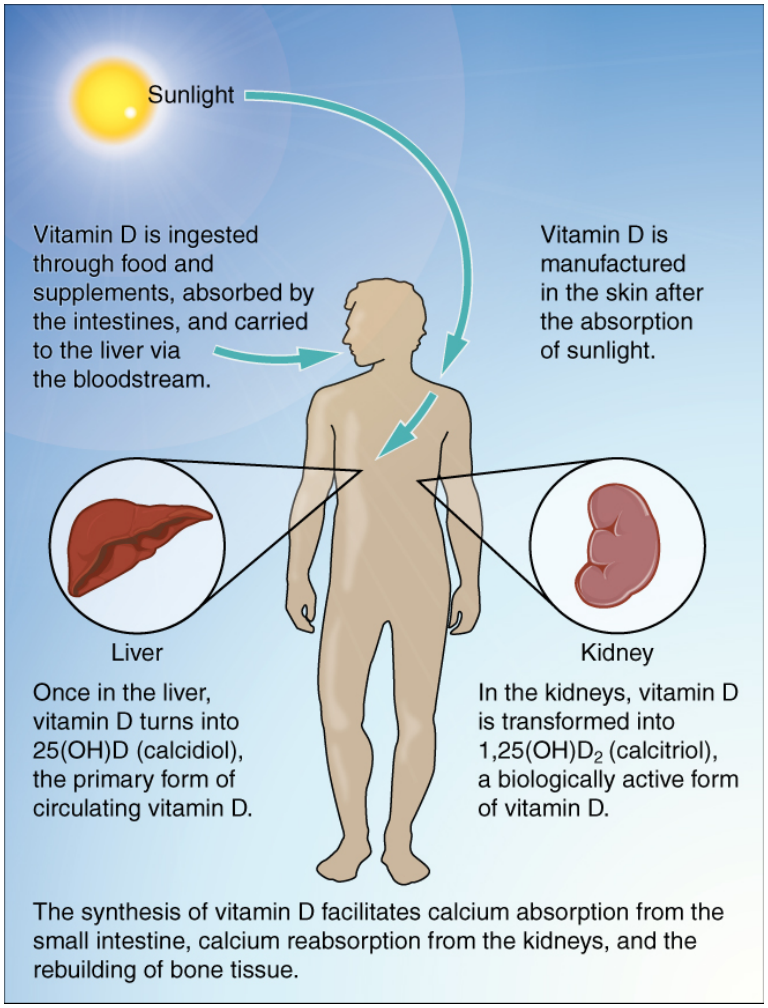


FIGURE 6.22 Synthesis of Vitamin D Sunlight is one source of vitamin D.

Other Nutrients

Vitamin K also supports bone mineralization and may have a synergistic role with vitamin D in the regulation of bone growth. Green leafy vegetables are a good source of vitamin K.

The minerals magnesium and fluoride may also play a role in supporting bone health. While magnesium is only found in trace amounts in the human body, more than 60 percent of it is in the skeleton, suggesting it plays a role in the structure of bone. Fluoride can displace the hydroxyl group in bone's hydroxyapatite crystals and form fluorapatite. Similar to its effect on dental enamel, fluorapatite helps stabilize and strengthen bone mineral. Fluoride can also enter spaces within hydroxyapatite crystals, thus increasing their density.

Omega-3 fatty acids have long been known to reduce inflammation in various parts of the body. Inflammation can interfere with the function of osteoblasts, so consuming omega-3 fatty acids, in the diet or in supplements, may also help enhance production of new osseous tissue. Table 6.5 summarizes the role of nutrients in bone health.

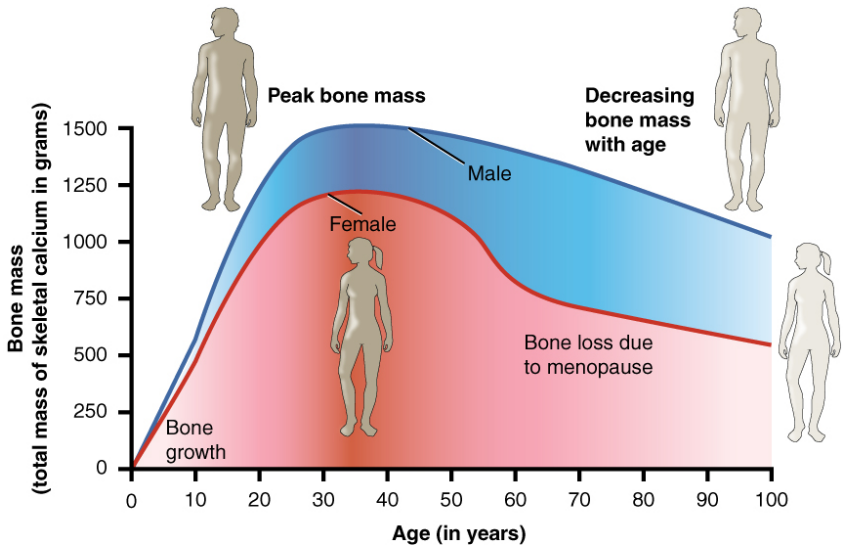


FIGURE 6.23 Graph Showing Relationship Between Age and Bone Mass Bone density peaks at about 30 years of age. Females lose bone mass more rapidly than males.

While osteoporosis can involve any bone, it most commonly affects the proximal ends of the femur, vertebrae, and wrist. As a result of the loss of bone density, the osseous tissue may not provide adequate support for everyday functions, and something as simple as a sneeze can cause a vertebral fracture. When an elderly person falls and breaks a hip (really, the femur), it is very likely the femur that broke first, which resulted in the fall. Histologically, osteoporosis is characterized by a reduction in the thickness of compact bone and the number and size of trabeculae in cancellous bone.

Figure 6.23 shows that females lose bone mass more quickly than males starting at about 50 years of age. This occurs because 50 is the approximate age at which females go through menopause. Not only do their menstrual periods lessen and eventually cease, but their ovaries reduce in size and then cease the production of estrogen, a hormone that promotes osteoblastic activity and production of bone matrix. Thus, osteoporosis is more common in females, but males can develop it, too. Anyone with a family history of osteoporosis has a greater risk of developing the disease, so the best treatment is prevention, which should start with a childhood diet that includes adequate intake of calcium and vitamin D and a lifestyle that includes weight-bearing exercise. These actions, as discussed above, are important in building bone mass. Promoting proper nutrition and weight-bearing exercise early in life can maximize bone mass before the age of 30, thus reducing the risk of osteoporosis.

For many elderly people, a hip fracture can be life threatening. The fracture itself may not be serious, but the immobility that comes during the healing process can lead to the formation of blood clots that can lodge in the capillaries of the lungs, resulting in respiratory failure; pneumonia due to the lack of poor air exchange that accompanies immobility; pressure sores (bed sores) that allow pathogens to enter the body and cause infections; and urinary tract infections from catheterization.

Current treatments for managing osteoporosis include bisphosphonates (the same medications often used in Paget's disease), calcitonin, and estrogen (for females only). Minimizing the risk of falls, for example, by removing tripping hazards, is also an important step in managing the potential outcomes from the disease.

Hormones That Influence Osteoclasts

Bone modeling and remodeling require osteoclasts to resorb unneeded, damaged, or old bone, and osteoblasts to lay down new bone. Two hormones that affect the osteoclasts are parathyroid hormone (PTH) and calcitonin.

PTH stimulates osteoclast proliferation and activity. As a result, calcium is released from the bones into the circulation, thus increasing the calcium ion concentration in the blood. PTH also promotes the reabsorption of calcium by the kidney tubules, which can affect calcium homeostasis (see below).

The small intestine is also affected by PTH, albeit indirectly. Because another function of PTH is to stimulate the

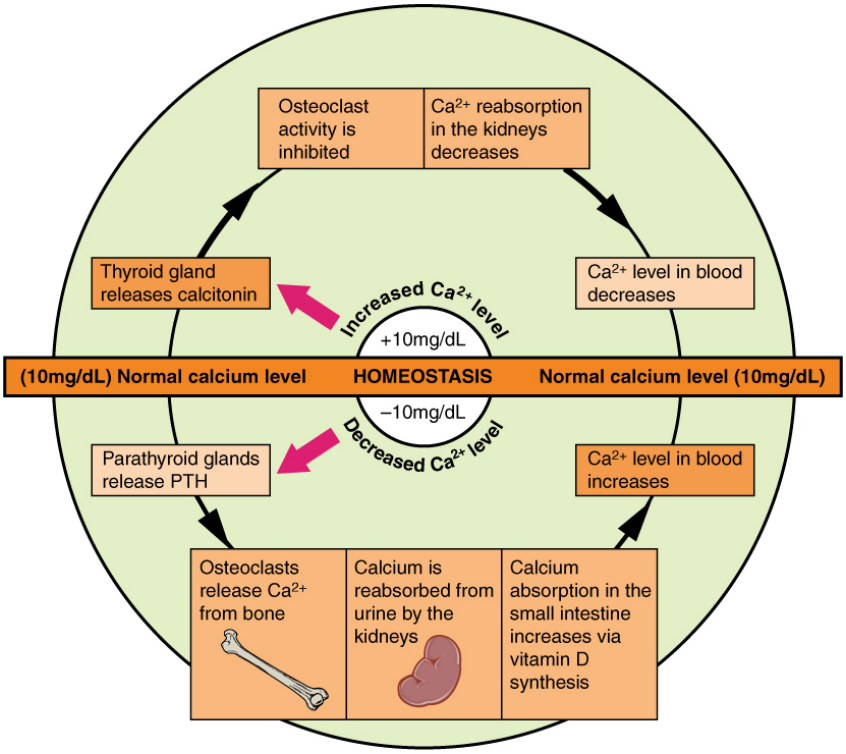


FIGURE 6.24 Pathways in Calcium Homeostasis The body regulates calcium homeostasis with two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated.

Calcium is a chemical element that cannot be produced by any biological processes. The only way it can enter the body is through the diet. The bones act as a storage site for calcium: The body deposits calcium in the bones when blood levels get too high, and it releases calcium when blood levels drop too low. This process is regulated by PTH, vitamin D, and calcitonin.

Cells of the parathyroid gland have plasma membrane receptors for calcium. When calcium is not binding to these receptors, the cells release PTH, which stimulates osteoclast proliferation and resorption of bone by osteoclasts. This demineralization process releases calcium into the blood. PTH promotes reabsorption of calcium from the urine by the kidneys, so that the calcium returns to the blood. Finally, PTH stimulates the synthesis of vitamin D, which in turn, stimulates calcium absorption from any digested food in the small intestine.

When all these processes return blood calcium levels to normal, there is enough calcium to bind with the receptors on the surface of the cells of the parathyroid glands, and this cycle of events is turned off (Figure 6.24).

When blood levels of calcium get too high, the thyroid gland is stimulated to release calcitonin (Figure 6.24), which inhibits osteoclast activity and stimulates calcium uptake by the bones, but also decreases reabsorption of calcium by the kidneys. All of these actions lower blood levels of calcium. When blood calcium levels return to normal, the thyroid gland stops secreting calcitonin.

surface of bone and continuous with ligaments

primary ossification center region, deep in the periosteal collar, where bone development starts during endochondral ossification

projection bone markings where part of the surface sticks out above the rest of the surface, where tendons and ligaments attach

proliferative zone region of the epiphyseal plate that makes new chondrocytes to replace those that die at the diaphyseal end of the plate and contributes to longitudinal growth of the epiphyseal plate

red marrow connective tissue in the interior cavity of a bone where hematopoiesis takes place

remodeling process by which osteoclasts resorb old or damaged bone at the same time as and on the same surface where osteoblasts form new bone to replace that which is resorbed

reserve zone region of the epiphyseal plate that anchors the plate to the osseous tissue of the epiphysis

secondary ossification center region of bone development in the epiphyses

sesamoid bone small, round bone embedded in a tendon; protects the tendon from compressive forces

short bone cube-shaped bone that is approximately equal in length, width, and thickness; provides limited motion

skeletal system organ system composed of bones and cartilage that provides for movement, support, and protection

spongy bone (also, cancellous bone) trabeculated osseous tissue that supports shifts in weight distribution

trabeculae (singular = trabecula) spikes or sections of the lattice-like matrix in spongy bone

yellow marrow connective tissue in the interior cavity of a bone where fat is stored

zone of calcified matrix region of the epiphyseal plate closest to the diaphyseal end; functions to connect the epiphyseal plate to the diaphysis

zone of maturation and hypertrophy region of the epiphyseal plate where chondrocytes from the proliferative zone grow and mature and contribute to the longitudinal growth of the epiphyseal plate

Chapter Review

6.1 The Functions of the Skeletal System

The major functions of the bones are body support, facilitation of movement, protection of internal organs, storage of minerals and fat, and hematopoiesis. Together, the muscular system and skeletal system are known as the musculoskeletal system.

6.2 Bone Classification

Bones can be classified according to their shapes. Long bones, such as the femur, are longer than they are wide. Short bones, such as the carpals, are approximately equal in length, width, and thickness. Flat bones are thin, but are often curved, such as the ribs. Irregular bones such as those of the face have no characteristic shape. Sesamoid bones, such as the patellae, are small and round, and are located in tendons.

6.3 Bone Structure

A hollow medullary cavity filled with yellow marrow runs the length of the diaphysis of a long bone. The walls of the diaphysis are compact bone. The epiphyses, which are wider sections at each end of a long bone, are filled with spongy bone and red marrow. The epiphyseal plate, a layer of hyaline cartilage, is replaced by osseous tissue as the organ grows in length. The medullary cavity has a delicate membranous lining called the endosteum. The outer surface of bone, except in regions covered with articular cartilage, is covered with a fibrous membrane called the periosteum. Flat bones consist of two layers of compact bone surrounding a layer of spongy bone. Bone markings depend on the function and location of bones. Articulations are places where two bones meet. Projections stick out from the surface of the bone and provide attachment points for tendons and ligaments. Holes are openings or depressions in the bones.

Bone matrix consists of collagen fibers and organic ground substance, primarily hydroxyapatite formed from calcium salts. Osteogenic cells develop into osteoblasts. Osteoblasts are cells that make new bone. They become osteocytes, the cells of mature bone, when they get trapped in the matrix. Osteoclasts engage in bone resorption. Compact bone is dense and composed of osteons, while spongy bone is less dense and made up of trabeculae. Blood vessels and nerves enter the bone through the nutrient foramina to nourish and innervate bones.

6.4 Bone Formation and Development

All bone formation is a replacement process. Embryos develop a cartilaginous skeleton and various membranes. During development, these are replaced by bone during the ossification process. In intramembranous ossification, bone develops directly

5. Which of the following can be found in areas of movement?
   a. hematopoiesis
   b. cartilage
   c. yellow marrow
   d. red marrow

6. The skeletal system is made of _____.
   a. muscles and tendons
   b. bones and cartilage
   c. vitreous humor
   d. minerals and fat

7. Most of the bones of the arms and hands are long bones; however, the bones in the wrist are categorized as _____.
   a. flat bones
   b. short bones
   c. sesamoid bones
   d. irregular bones

8. Sesamoid bones are found embedded in _____.
   a. joints
   b. muscles
   c. ligaments
   d. tendons

9. Bones that surround the spinal cord are classified as _____ bones.
   a. irregular
   b. sesamoid
   c. flat
   d. short

10. Which category of bone is among the most numerous in the skeleton?
   a. long bone
   b. sesamoid bone
   c. short bone
   d. flat bone

11. Long bones enable body movement by acting as a _____.
   a. counterweight
   b. resistive force
   c. lever
   d. fulcrum

12. Which of the following occurs in the spongy bone of the epiphysis?
   a. bone growth
   b. bone remodeling
   c. hematopoiesis
   d. shock absorption

13. The diaphysis contains _____.
   a. the metaphysis
   b. fat stores
   c. spongy bone
   d. compact bone

14. The fibrous membrane covering the outer surface of the bone is the _____.
   a. periosteum
   b. epiphysis
   c. endosteum
   d. diaphysis

15. Which of the following are incapable of undergoing mitosis?
   a. osteoblasts and osteoclasts
   b. osteocytes and osteoclasts
   c. osteoblasts and osteocytes
   d. osteogenic cells and osteoclasts

16. Which cells do not originate from osteogenic cells?
   a. osteoblasts
   b. osteoclasts
   c. osteocytes
   d. osteoprogenitor cells

17. Which of the following are found in compact bone and cancellous bone?
   a. Haversian systems
   b. Haversian canals
   c. lamellae
   d. lacunae

18. Which of the following are *only* found in cancellous bone?
   a. canaliculi
   b. Volkmann's canals
   c. trabeculae
   d. calcium salts

19. The area of a bone where the nutrient foramen passes forms what kind of bone marking?
   a. a hole
   b. a facet
   c. a canal
   d. a fissure

20. Why is cartilage slow to heal?
   a. because it eventually develops into bone
   b. because it is semi-solid and flexible
   c. because it does not have a blood supply
   d. because endochondral ossification replaces all cartilage with bone

35. Which of the following hormones are responsible for the adolescent growth spurt?
   a. estrogen and testosterone
   b. calcitonin and calcitriol
   c. growth hormone and parathyroid hormone
   d. thyroxine and progesterone

36. With respect to their direct effects on osseous tissue, which pair of hormones has actions that oppose each other?
   a. estrogen and testosterone
   b. calcitonin and calcitriol
   c. estrogen and progesterone
   d. calcitonin and parathyroid hormone

37. When calcium levels are too high or too low, which body system is primarily affected?
   a. skeletal system
   b. endocrine system
   c. digestive system
   d. nervous system

38. All of the following play a role in calcium homeostasis except
   a. thyroxine
   b. calcitonin
   c. parathyroid hormone
   d. vitamin D

39. Which of the following is most likely to be released when blood calcium levels are elevated?
   a. thyroxine
   b. calcitonin
   c. parathyroid hormone
   d. vitamin D

Critical Thinking Questions

40. The skeletal system is composed of bone and cartilage and has many functions. Choose three of these functions and discuss what features of the skeletal system allow it to accomplish these functions.

41. What are the structural and functional differences between a tarsal and a metatarsal?

42. What are the structural and functional differences between the femur and the patella?

43. If the articular cartilage at the end of one of your long bones were to degenerate, what symptoms do you think you would experience? Why?

44. In what ways is the structural makeup of compact and spongy bone well suited to their respective functions?

45. In what ways do intramembranous and endochondral ossification differ?

46. Considering how a long bone develops, what are the similarities and differences between a primary and a secondary ossification center?

47. What is the difference between closed reduction and open reduction? In what type of fracture would closed reduction most likely occur? In what type of fracture would open reduction most likely occur?

48. In terms of origin and composition, what are the differences between an internal callus and an external callus?

49. If you were a dietician who had a young female patient with a family history of osteoporosis, what foods would you suggest she include in her diet? Why?

50. During the early years of space exploration our astronauts, who had been floating in space, would return to earth showing significant bone loss dependent on how long they were in space. Discuss how this might happen and what could be done to alleviate this condition.

51. An individual with very low levels of vitamin D presents themselves to you complaining of seemingly fragile bones. Explain how these might be connected.

52. Describe the effects caused when the parathyroid gland fails to respond to calcium bound to its receptors.

will cause bones to become thinner. This may happen during a prolonged hospital stay, following limb immobilization in a cast, or going into the weightlessness of outer space. Even a change in diet, such as eating only soft food due to the loss of teeth, will result in a noticeable decrease in the size and thickness of the jaw bones.

7.1 Divisions of the Skeletal System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the functions of the skeletal system
- Distinguish between the axial skeleton and appendicular skeleton
- Define the axial skeleton and its components
- Define the appendicular skeleton and its components

The skeletal system includes all of the bones, cartilages, and ligaments of the body that support and give shape to the body and body structures. The **skeleton** consists of the bones of the body. For adults, there are 206 bones in the skeleton. Younger individuals have higher numbers of bones because some bones fuse together during childhood and adolescence to form an adult bone. The primary functions of the skeleton are to provide a rigid, internal structure that can support the weight of the body against the force of gravity, and to provide a structure upon which muscles can act to produce movements of the body. The lower portion of the skeleton is specialized for stability during walking or running. In contrast, the upper skeleton has greater mobility and ranges of motion, features that allow you to lift and carry objects or turn your head and trunk.

In addition to providing for support and movements of the body, the skeleton has protective and storage functions. It protects the internal organs, including the brain, spinal cord, heart, lungs, and pelvic organs. The bones of the skeleton serve as the primary storage site for important minerals such as calcium and phosphate. The bone marrow found within bones stores fat and houses the blood-cell producing tissue of the body.

The skeleton is subdivided into two major divisions—the axial and appendicular.

The Axial Skeleton

The skeleton is subdivided into two major divisions—the axial and appendicular. The **axial skeleton** forms the vertical, central axis of the body and includes all bones of the head, neck, chest, and back (Figure 7.2). It serves to protect the brain, spinal cord, heart, and lungs. It also serves as the attachment site for muscles that move the head, neck, and back, and for muscles that act across the shoulder and hip joints to move their corresponding limbs.

The axial skeleton of the adult consists of 80 bones, including the **skull**, the **vertebral column**, and the **thoracic cage**. The skull is formed by 22 bones. Also associated with the head are an additional seven bones, including the **hyoid bone** and the **ear ossicles** (three small bones found in each middle ear). The vertebral column consists of 24 bones, each called a **vertebra**, plus the **sacrum** and **coccyx**. The thoracic cage includes the 12 pairs of **ribs**, and the **sternum**, the flattened bone of the anterior chest.

structures, form the nasal cavity, enclose the eyeballs, and support the teeth of the upper and lower jaws. The rounded brain case surrounds and protects the brain and houses the middle and inner ear structures.

In the adult, the skull consists of 22 individual bones, 21 of which are immobile and united into a single unit. The 22nd bone is the **mandible** (lower jaw), which is the only moveable bone of the skull.

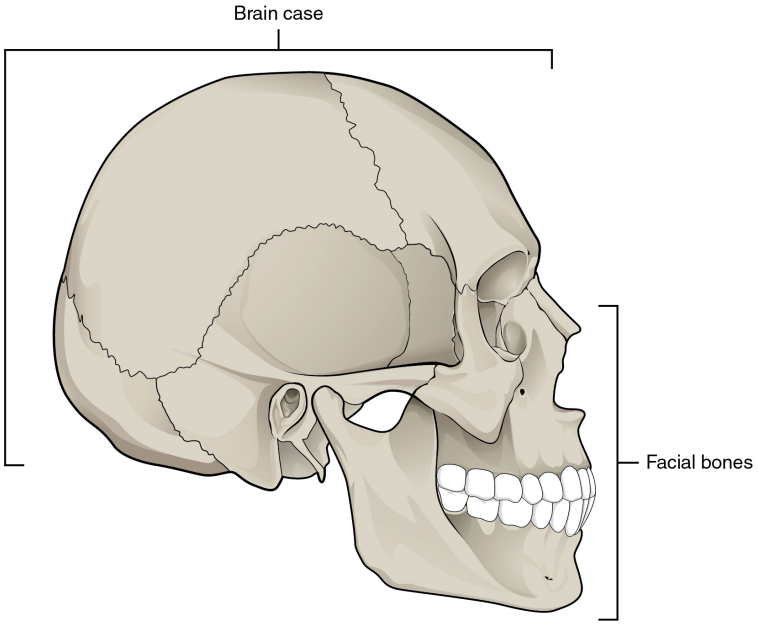


FIGURE 7.3 Parts of the Skull The skull consists of the rounded brain case that houses the brain and the facial bones that form the upper and lower jaws, nose, orbits, and other facial structures.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/skull1) to view a rotating and exploded skull, with color-coded bones. Which bone (yellow) is centrally located and joins with most of the other bones of the skull?

Anterior View of Skull

The anterior skull consists of the facial bones and provides the bony support for the eyes and structures of the face. This view of the skull is dominated by the openings of the orbits and the nasal cavity. Also seen are the upper and lower jaws, with their respective teeth (Figure 7.4).

The **orbit** is the bony socket that houses the eyeball and muscles that move the eyeball or open the upper eyelid. The upper margin of the anterior orbit is the **supraorbital margin**. Located near the midpoint of the supraorbital margin is a small opening called the **supraorbital foramen**. This provides for passage of a sensory nerve to the skin of the forehead. Below the orbit is the **infraorbital foramen**, which is the point of emergence for a sensory nerve that supplies the anterior face below the orbit.

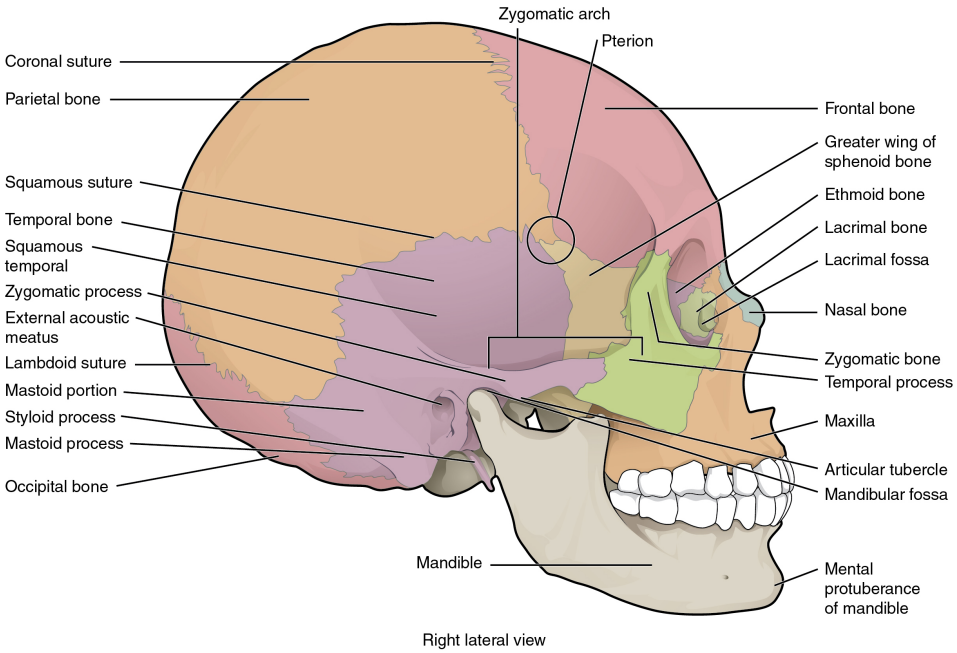


FIGURE 7.5 Lateral View of Skull The lateral skull shows the large rounded brain case, zygomatic arch, and the upper and lower jaws. The zygomatic arch is formed jointly by the zygomatic process of the temporal bone and the temporal process of the zygomatic bone. The shallow space above the zygomatic arch is the temporal fossa. The space inferior to the zygomatic arch and deep to the posterior mandible is the infratemporal fossa.

Bones of the Brain Case

The brain case contains and protects the brain. The interior space that is almost completely occupied by the brain is called the **cranial cavity**. This cavity is bounded superiorly by the rounded top of the skull, which is called the **calvaria** (skullcap), and the lateral and posterior sides of the skull. The bones that form the top and sides of the brain case are usually referred to as the "flat" bones of the skull.

The floor of the brain case is referred to as the base of the skull. This is a complex area that varies in depth and has numerous openings for the passage of cranial nerves, blood vessels, and the spinal cord. Inside the skull, the base is subdivided into three large spaces, called the **anterior cranial fossa**, **middle cranial fossa**, and **posterior cranial fossa** (fossa = "trench or ditch") (Figure 7.6). From anterior to posterior, the fossae increase in depth. The shape and depth of each fossa corresponds to the shape and size of the brain region that each houses. The boundaries and openings of the cranial fossae (singular = fossa) will be described in a later section.

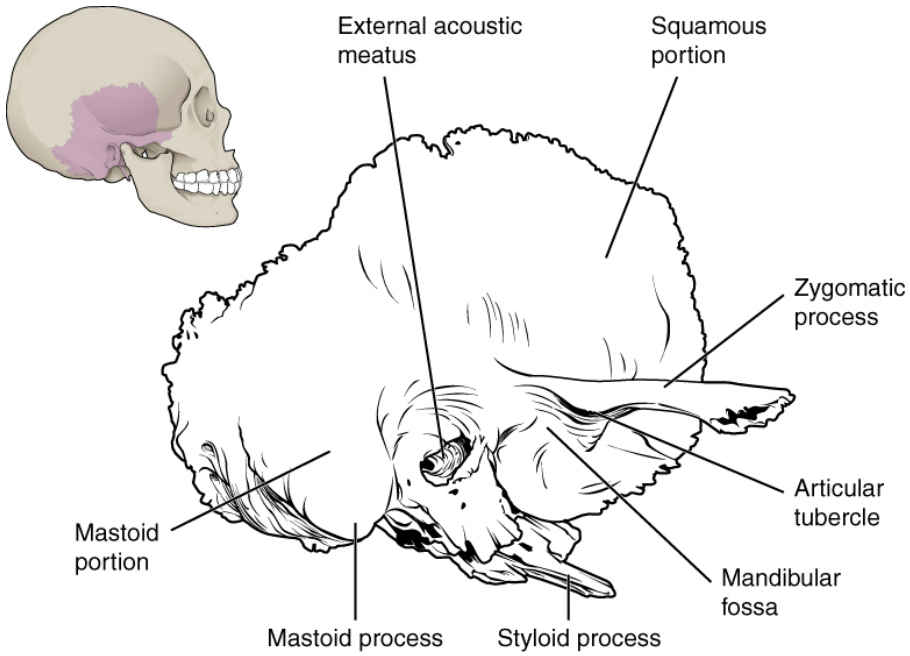


FIGURE 7.7 Temporal Bone A lateral view of the isolated temporal bone shows the squamous, mastoid, and zygomatic portions of the temporal bone.

Important landmarks of the temporal bone, as shown in Figure 7.8, include the following:

- **External acoustic meatus** (ear canal)—This is the large opening on the lateral side of the skull that is associated with the ear.
- **Internal acoustic meatus**—This opening is located inside the cranial cavity, on the medial side of the petrous ridge. It connects to the middle and inner ear cavities of the temporal bone.
- **Mandibular fossa**—This is the deep, oval-shaped depression located on the external base of the skull, just in front of the external acoustic meatus. The mandible (lower jaw) joins with the skull at this site as part of the temporomandibular joint, which allows for movements of the mandible during opening and closing of the mouth.
- **Articular tubercle**—The smooth ridge located immediately anterior to the mandibular fossa. Both the articular tubercle and mandibular fossa contribute to the temporomandibular joint, the joint that provides for movements between the temporal bone of the skull and the mandible.
- **Styloid process**—Posterior to the mandibular fossa on the external base of the skull is an elongated, downward bony projection called the styloid process, so named because of its resemblance to a stylus (a pen or writing tool). This structure serves as an attachment site for several small muscles and for a ligament that supports the hyoid bone of the neck. (See also Figure 7.7.)
- **Stylomastoid foramen**—This small opening is located between the styloid process and mastoid process. This is the point of exit for the cranial nerve that supplies the facial muscles.
- **Carotid canal**—The carotid canal is a zig-zag shaped tunnel that provides passage through the base of the skull for one of the major arteries that supplies the brain. Its entrance is located on the outside base of the skull, anteromedial to the styloid process. The canal then runs anteromedially within the bony base of the skull, and then turns upward to its exit in the floor of the middle cranial cavity, above the foramen lacerum.

ridges. These are located just behind your eyebrows and vary in size among individuals, although they are generally larger in males. Inside the cranial cavity, the frontal bone extends posteriorly. This flattened region forms both the roof of the orbit below and the floor of the anterior cranial cavity above (see Figure 7.8**b**).

Occipital Bone

The **occipital bone** is the single bone that forms the posterior skull and posterior base of the cranial cavity (Figure 7.9; see also Figure 7.8). On its outside surface, at the posterior midline, is a small protrusion called the **external occipital protuberance**, which serves as an attachment site for a ligament of the posterior neck. Lateral to either side of this bump is a **superior nuchal line** (nuchal = "nape" or "posterior neck"). The nuchal lines represent the most superior point at which muscles of the neck attach to the skull, with only the scalp covering the skull above these lines. On the base of the skull, the occipital bone contains the large opening of the **foramen magnum**, which allows for passage of the spinal cord as it exits the skull. On either side of the foramen magnum is an oval-shaped **occipital condyle**. These condyles form joints with the first cervical vertebra and thus support the skull on top of the vertebral column.

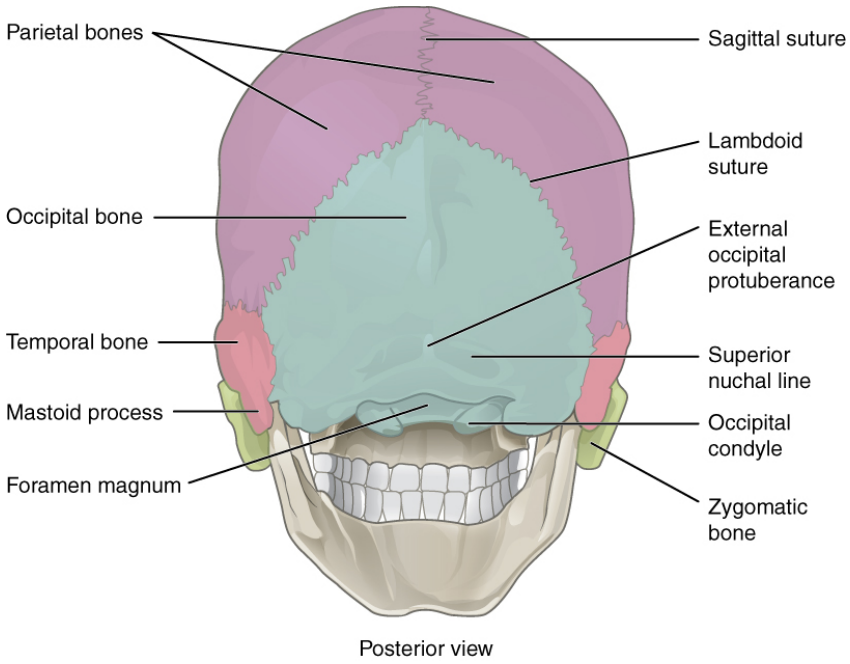


FIGURE 7.9 Posterior View of Skull This view of the posterior skull shows attachment sites for muscles and joints that support the skull.

Sphenoid Bone

The **sphenoid bone** is a single, complex bone of the central skull (Figure 7.10). It serves as a "keystone" bone, because it joins with almost every other bone of the skull. The sphenoid forms much of the base of the central skull (see Figure 7.8) and also extends laterally to contribute to the sides of the skull (see Figure 7.5). Inside the cranial cavity, the right and left **lesser wings of the sphenoid bone**, which resemble the wings of a flying bird, form the lip of a prominent ridge that marks the boundary between the anterior and middle cranial fossae. The **sella turcica** ("Turkish saddle") is located at the midline of the middle cranial fossa. This bony region of the sphenoid bone is named for its resemblance to the horse saddles used by the Ottoman Turks, with a high back and a tall front. The rounded depression in the floor of the sella turcica is the **hypophyseal (pituitary) fossa**, which houses the pea-sized pituitary (hypophyseal) gland. The **greater wings of the sphenoid bone** extend laterally to either side away from the sella turcica, where they form the anterior floor of the middle cranial fossa. The greater wing is best seen on the outside of the lateral skull, where it forms a rectangular area immediately anterior to the squamous portion of the temporal bone.

On the inferior aspect of the skull, each half of the sphenoid bone forms two thin, vertically oriented bony plates. These are the **medial pterygoid plate** and **lateral pterygoid plate** (pterygoid = "wing-shaped"). The right and left medial pterygoid plates form the posterior, lateral walls of the nasal cavity. The somewhat larger lateral pterygoid plates serve as attachment sites for chewing muscles that fill the infratemporal space and act on the mandible.

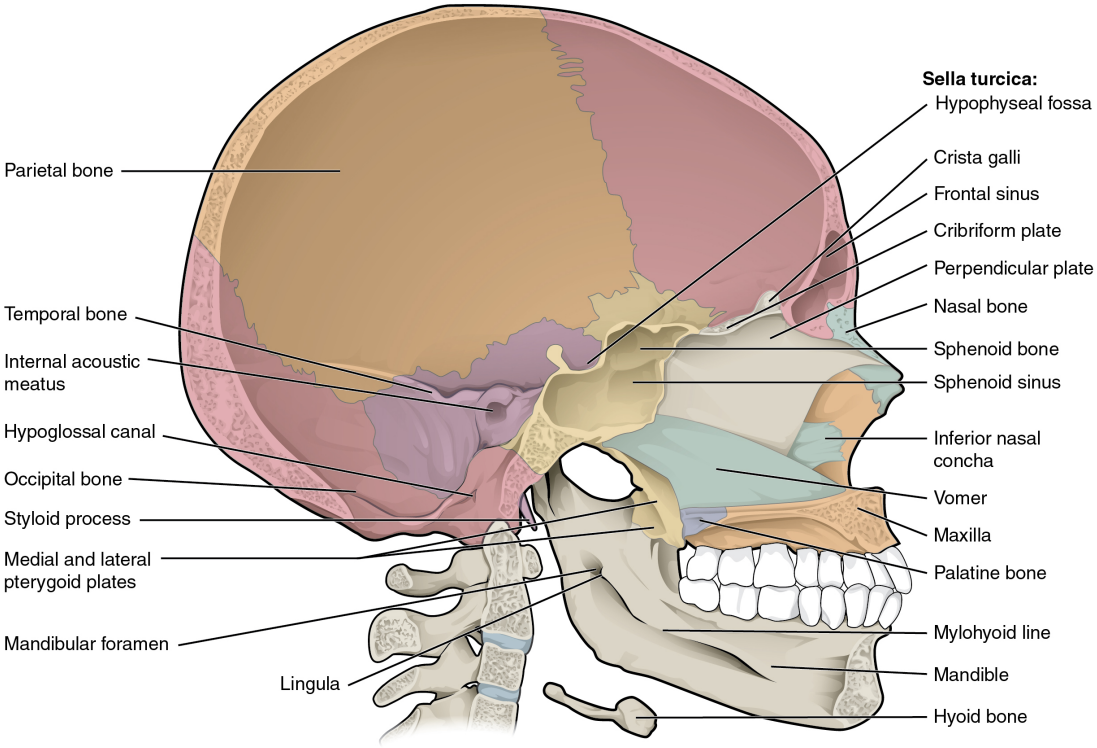


FIGURE 7.11 Sagittal Section of Skull This midline view of the sagittally sectioned skull shows the nasal septum.

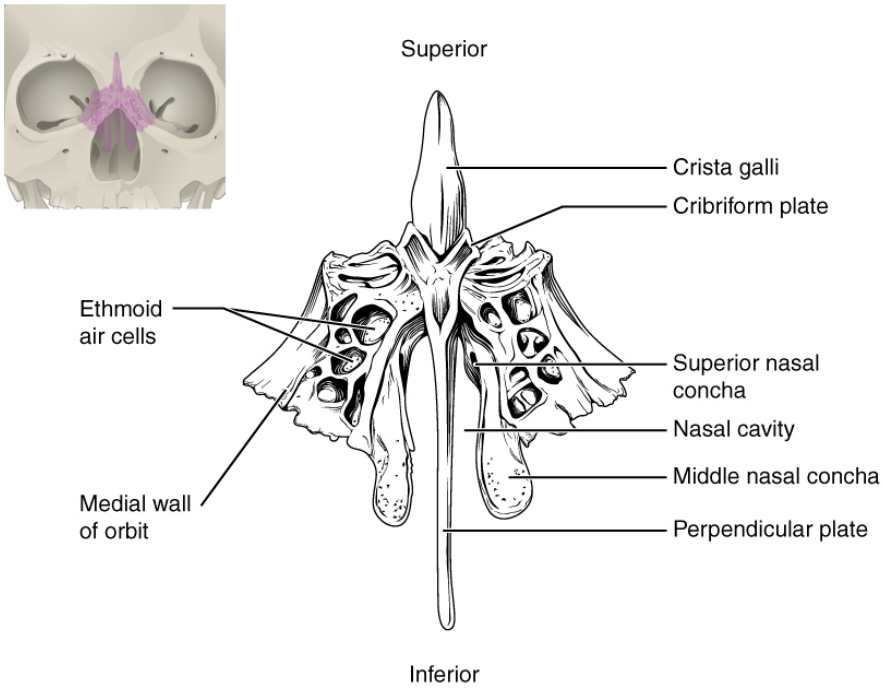


FIGURE 7.12 Ethmoid Bone The unpaired ethmoid bone is located at the midline within the central skull. It has an upward projection, the crista galli, and a downward projection, the perpendicular plate, which forms the upper nasal septum. The cribriform plates form both the roof of the nasal cavity and a portion of the anterior cranial fossa floor. The lateral sides of the ethmoid bone form the lateral walls of the upper nasal cavity, part of the medial orbit wall, and give rise to the superior and middle nasal conchae. The ethmoid bone also contains the ethmoid air cells.

Strong blows to the brain-case portion of the skull can produce fractures. These may result in bleeding inside the skull with subsequent injury to the brain. The most common is a linear skull fracture, in which fracture lines radiate from the point of impact. Other fracture types include a comminuted fracture, in which the bone is broken into several pieces at the point of impact, or a depressed fracture, in which the fractured bone is pushed inward. In a contrecoup (counterblow) fracture, the bone at the point of impact is not broken, but instead a fracture occurs on the opposite side of the skull. Fractures of the occipital bone at the base of the skull can occur in this manner, producing a basilar fracture that can damage the artery that passes through the carotid canal.

A blow to the lateral side of the head may fracture the bones of the pterion. The pterion is an important clinical landmark because located immediately deep to it on the inside of the skull is a major branch of an artery that supplies the skull and covering layers of the brain. A strong blow to this region can fracture the bones around the pterion. If the underlying artery is damaged, bleeding can cause the formation of a hematoma (collection of blood) between the brain and interior of the skull. As blood accumulates, it will put pressure on the brain. Symptoms associated with a hematoma may not be apparent immediately following the injury, but if untreated, blood accumulation will exert increasing pressure on the brain and can result in death within a few hours.

INTERACTIVE LINK

View this animation (http://openstax.org/l/headblow) to see how a blow to the head may produce a contrecoup (counterblow) fracture of the basilar portion of the occipital bone on the base of the skull. Why may a basilar fracture be life threatening?

Facial Bones of the Skull

The facial bones of the skull form the upper and lower jaws, the nose, nasal cavity and nasal septum, and the orbit. The facial bones include 14 bones, with six paired bones and two unpaired bones. The paired bones are the maxilla, palatine, zygomatic, nasal, lacrimal, and inferior nasal conchae bones. The unpaired bones are the vomer and mandible bones. Although classified with the brain-case bones, the ethmoid bone also contributes to the nasal septum and the walls of the nasal cavity and orbit.

Maxillary Bone

The **maxillary bone**, often referred to simply as the maxilla (plural = maxillae), is one of a pair that together form the upper jaw, much of the hard palate, the medial floor of the orbit, and the lateral base of the nose (see Figure 7.4). The curved, inferior margin of the maxillary bone that forms the upper jaw and contains the upper teeth is the **alveolar process of the maxilla** (Figure 7.14). Each tooth is anchored into a deep socket called an alveolus. On the anterior maxilla, just below the orbit, is the infraorbital foramen. This is the point of exit for a sensory nerve that supplies the nose, upper lip, and anterior cheek. On the inferior skull, the **palatine process** from each maxillary bone can be seen joining together at the midline to form the anterior three-quarters of the hard palate (see Figure 7.8**a**). The **hard palate** is the bony plate that forms the roof of the mouth and floor of the nasal cavity, separating the oral and nasal cavities.

Zygomatic Bone

The **zygomatic bone** is also known as the cheekbone. Each of the paired zygomatic bones forms much of the lateral wall of the orbit and the lateral-inferior margins of the anterior orbital opening (see Figure 7.4). The short temporal process of the zygomatic bone projects posteriorly, where it forms the anterior portion of the zygomatic arch (see Figure 7.5).

Nasal Bone

The **nasal bone** is one of two small bones that articulate (join) with each other to form the bony base (bridge) of the nose. They also support the cartilages that form the lateral walls of the nose (see Figure 7.11). These are the bones that are damaged when the nose is broken.

Lacrimal Bone

Each **lacrimal bone** is a small, rectangular bone that forms the anterior, medial wall of the orbit (see Figure 7.4 and Figure 7.5). The anterior portion of the lacrimal bone forms a shallow depression called the **lacrimal fossa**, and extending inferiorly from this is the **nasolacrimal canal**. The lacrimal fluid (tears of the eye), which serves to maintain the moist surface of the eye, drains at the medial corner of the eye into the nasolacrimal canal. This duct then extends downward to open into the nasal cavity, behind the inferior nasal concha. In the nasal cavity, the lacrimal fluid normally drains posteriorly, but with an increased flow of tears due to crying or eye irritation, some fluid will also drain anteriorly, thus causing a runny nose.

Inferior Nasal Conchae

The right and left inferior nasal conchae form a curved bony plate that projects into the nasal cavity space from the lower lateral wall (see Figure 7.13). The inferior concha is the largest of the nasal conchae and can easily be seen when looking into the anterior opening of the nasal cavity.

Vomer Bone

The unpaired vomer bone, often referred to simply as the vomer, is triangular-shaped and forms the posterior-inferior part of the nasal septum (see Figure 7.11). The vomer is best seen when looking from behind into the posterior openings of the nasal cavity (see Figure 7.8**a**). In this view, the vomer is seen to form the entire height of the nasal septum. A much smaller portion of the vomer can also be seen when looking into the anterior opening of the nasal cavity.

Mandible

The **mandible** forms the lower jaw and is the only moveable bone of the skull. At the time of birth, the mandible consists of paired right and left bones, but these fuse together during the first year to form the single U-shaped mandible of the adult skull. Each side of the mandible consists of a horizontal body and posteriorly, a vertically oriented **ramus of the mandible** (ramus = “branch”). The outside margin of the mandible, where the body and ramus come together is called the **angle of the mandible** (Figure 7.15).

The ramus on each side of the mandible has two upward-going bony projections. The more anterior projection is the flattened **coronoid process of the mandible**, which provides attachment for one of the biting muscles. The posterior projection is the **condylar process of the mandible**, which is topped by the oval-shaped **condyle**. The condyle of the mandible articulates (joins) with the mandibular fossa and articular tubercle of the temporal bone. Together these articulations form the temporomandibular joint, which allows for opening and closing of the mouth (see Figure 7.5). The broad U-shaped curve located between the coronoid and condylar processes is the **mandibular notch**.

Important landmarks for the mandible include the following:

- **Alveolar process of the mandible**—This is the upper border of the mandibular body and serves to anchor the lower teeth.
- **Mental protuberance**—The forward projection from the inferior margin of the anterior mandible that forms the chin (mental = “chin”).
- **Mental foramen**—The opening located on each side of the anterior-lateral mandible, which is the exit site for a sensory nerve that supplies the chin.
- **Mylohyoid line**—This bony ridge extends along the inner aspect of the mandibular body (see Figure 7.11). The muscle that forms the floor of the oral cavity attaches to the mylohyoid lines on both sides of the mandible.
- **Mandibular foramen**—This opening is located on the medial side of the ramus of the mandible. The opening

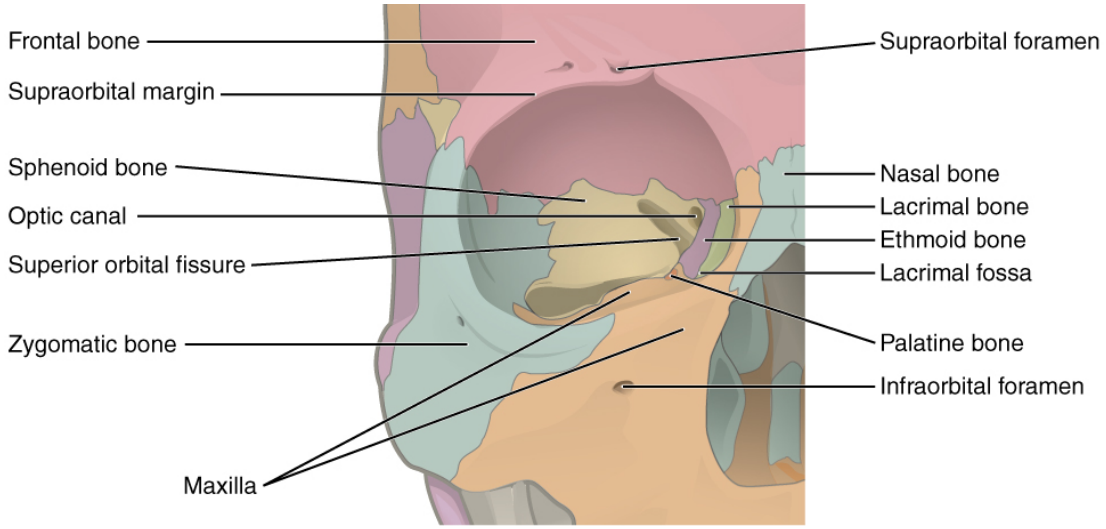


FIGURE 7.16 Bones of the Orbit Seven skull bones contribute to the walls of the orbit. Opening into the posterior orbit from the cranial cavity are the optic canal and superior orbital fissure.

The Nasal Septum and Nasal Conchae

The **nasal septum** consists of both bone and cartilage components (Figure 7.17; see also Figure 7.11). The upper portion of the septum is formed by the perpendicular plate of the ethmoid bone. The lower and posterior parts of the septum are formed by the triangular-shaped vomer bone. In an anterior view of the skull, the perpendicular plate of the ethmoid bone is easily seen inside the nasal opening as the upper nasal septum, but only a small portion of the vomer is seen as the inferior septum. A better view of the vomer bone is seen when looking into the posterior nasal cavity with an inferior view of the skull, where the vomer forms the full height of the nasal septum. The anterior nasal septum is formed by the **septal cartilage**, a flexible plate that fills in the gap between the perpendicular plate of the ethmoid and vomer bones. This cartilage also extends outward into the nose where it separates the right and left nostrils. The septal cartilage is not found in the dry skull.

Attached to the lateral wall on each side of the nasal cavity are the superior, middle, and inferior **nasal conchae** (singular = concha), which are named for their positions (see Figure 7.13). These are bony plates that curve downward as they project into the space of the nasal cavity. They serve to swirl the incoming air, which helps to warm and moisturize it before the air moves into the delicate air sacs of the lungs. This also allows mucus, secreted by the tissue lining the nasal cavity, to trap incoming dust, pollen, bacteria, and viruses. The largest of the conchae is the inferior nasal concha, which is an independent bone of the skull. The middle concha and the superior conchae, which is the smallest, are both formed by the ethmoid bone. When looking into the anterior nasal opening of the skull, only the inferior and middle conchae can be seen. The small superior nasal concha is well hidden above and behind the middle concha.

- **Foramen rotundum**—This rounded opening (rotundum = "round") is located in the floor of the middle cranial fossa, just inferior to the superior orbital fissure. It is the exit point for a major sensory nerve that supplies the cheek, nose, and upper teeth.
- **Foramen ovale of the middle cranial fossa**—This large, oval-shaped opening in the floor of the middle cranial fossa provides passage for a major sensory nerve to the lateral head, cheek, chin, and lower teeth.
- **Foramen spinosum**—This small opening, located posterior-lateral to the foramen ovale, is the entry point for an important artery that supplies the covering layers surrounding the brain. The branching pattern of this artery forms readily visible grooves on the internal surface of the skull and these grooves can be traced back to their origin at the foramen spinosum.
- **Carotid canal**—This is the zig-zag passageway through which a major artery to the brain enters the skull. The entrance to the carotid canal is located on the inferior aspect of the skull, anteromedial to the styloid process (see Figure 7.8**a**). From here, the canal runs anteromedially within the bony base of the skull. Just above the foramen lacerum, the carotid canal opens into the middle cranial cavity, near the posterior-lateral base of the sella turcica.
- **Foramen lacerum**—This irregular opening is located in the base of the skull, immediately inferior to the exit of the carotid canal. This opening is an artifact of the dry skull, because in life it is completely filled with cartilage. All the openings of the skull that provide for passage of nerves or blood vessels have smooth margins; the word lacerum ("ragged" or "torn") tells us that this opening has ragged edges and thus nothing passes through it.

Posterior Cranial Fossa

The posterior cranial fossa is the most posterior and deepest portion of the cranial cavity. It contains the cerebellum of the brain. The posterior fossa is bounded anteriorly by the petrous ridges, while the occipital bone forms the floor and posterior wall. It is divided at the midline by the large foramen magnum ("great aperture"), the opening that provides for passage of the spinal cord.

Located on the medial wall of the petrous ridge in the posterior cranial fossa is the internal acoustic meatus (see Figure 7.11). This opening provides for passage of the nerve from the hearing and equilibrium organs of the inner ear, and the nerve that supplies the muscles of the face. Located at the anterior-lateral margin of the foramen magnum is the **hypoglossal canal**. These emerge on the inferior aspect of the skull at the base of the occipital condyle and provide passage for an important nerve to the tongue.

Immediately inferior to the internal acoustic meatus is the large, irregularly shaped **jugular foramen** (see Figure 7.8**a**). Several cranial nerves from the brain exit the skull via this opening. It is also the exit point through the base of the skull for all the venous return blood leaving the brain. The venous structures that carry blood inside the skull form large, curved grooves on the inner walls of the posterior cranial fossa, which terminate at each jugular foramen.

Paranasal Sinuses

The **paranasal sinuses** are hollow, air-filled spaces located within certain bones of the skull (Figure 7.18). All of the sinuses communicate with the nasal cavity (paranasal = "next to nasal cavity") and are lined with nasal mucosa. They serve to reduce bone mass and thus lighten the skull, and they also add resonance to the voice. This second feature is most obvious when you have a cold or sinus congestion. These produce swelling of the mucosa and excess mucus production, which can obstruct the narrow passageways between the sinuses and the nasal cavity, causing your voice to sound different to yourself and others. This blockage can also allow the sinuses to fill with fluid, with the resulting pressure producing pain and discomfort.

The paranasal sinuses are named for the skull bone that each occupies. The **frontal sinus** is located just above the eyebrows, within the frontal bone (see Figure 7.17). This irregular space may be divided at the midline into bilateral spaces, or these may be fused into a single sinus space. The frontal sinus is the most anterior of the paranasal sinuses. The largest sinus is the **maxillary sinus**. These are paired and located within the right and left maxillary bones, where they occupy the area just below the orbits. The maxillary sinuses are most commonly involved during sinus infections. Because their connection to the nasal cavity is located high on their medial wall, they are difficult to drain. The **sphenoid sinus** is a single, midline sinus. It is located within the body of the sphenoid bone, just anterior and inferior to the sella turcica, thus making it the most posterior of the paranasal sinuses. The lateral aspects of the ethmoid bone contain multiple small spaces separated by very thin bony walls. Each of these spaces is called an **ethmoid air cell**. These are located on both sides of the ethmoid bone, between the upper nasal cavity and medial

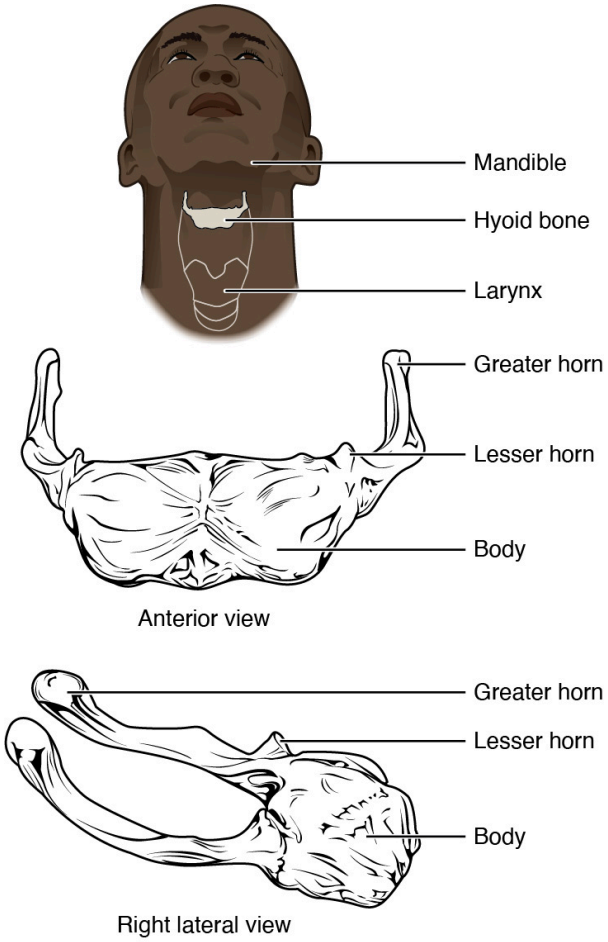


FIGURE 7.19 Hyoid Bone The hyoid bone is located in the upper neck and does not join with any other bone. It provides attachments for muscles that act on the tongue, larynx, and pharynx.

7.3 The Vertebral Column

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe each region of the vertebral column and the number of bones in each region
- Discuss the curves of the vertebral column and how these change after birth
- Describe a typical vertebra and determine the distinguishing characteristics for vertebrae in each vertebral region and features of the sacrum and the coccyx
- Define the structure of an intervertebral disc
- Determine the location of the ligaments that provide support for the vertebral column

The vertebral column is also known as the spinal column or spine (Figure 7.20). It consists of a sequence of vertebrae (singular = vertebra), each of which is separated and united by an **intervertebral disc**. Together, the vertebrae and intervertebral discs form the vertebral column. It is a flexible column that supports the head, neck, and body and allows for their movements. It also protects the spinal cord, which passes down the back through openings in the vertebrae.

During fetal development, the body is flexed anteriorly into the fetal position, giving the entire vertebral column a single curvature that is concave anteriorly. In the adult, this fetal curvature is retained in two regions of the vertebral column as the **thoracic curve**, which involves the thoracic vertebrae, and the **sacrococcygeal curve**, formed by the sacrum and coccyx. Each of these is thus called a **primary curve** because they are retained from the original fetal curvature of the vertebral column.

A **secondary curve** develops gradually after birth as the child learns to sit upright, stand, and walk. Secondary curves are concave posteriorly, opposite in direction to the original fetal curvature. The **cervical curve** of the neck region develops as the infant begins to hold their head upright when sitting. Later, as the child begins to stand and then to walk, the **lumbar curve** of the lower back develops. In adults, the lumbar curve is generally deeper in females.

Disorders associated with the curvature of the spine include **kyphosis** (an excessive posterior curvature of the thoracic region), **lordosis** (an excessive anterior curvature of the lumbar region), and **scoliosis** (an abnormal, lateral curvature, accompanied by twisting of the vertebral column).

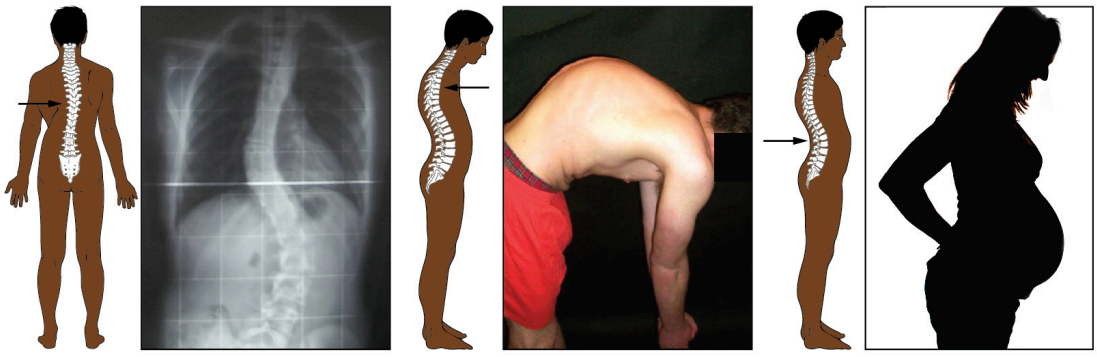
Disorders of the...

Vertebral Column

Developmental anomalies, pathological changes, or obesity can enhance the normal vertebral column curves, resulting in the development of abnormal or excessive curvatures (Figure 7.21). Kyphosis, also referred to as humpback or hunchback, is an excessive posterior curvature of the thoracic region. This can develop when osteoporosis causes weakening and erosion of the anterior portions of the upper thoracic vertebrae, resulting in their gradual collapse (Figure 7.22). Lordosis, or swayback, is an excessive anterior curvature of the lumbar region and is most commonly associated with obesity or late pregnancy. The accumulation of body weight in the abdominal region results an anterior shift in the line of gravity that carries the weight of the body. This causes in an anterior tilt of the pelvis and a pronounced enhancement of the lumbar curve.

Scoliosis is an abnormal, lateral curvature, accompanied by twisting of the vertebral column. Compensatory curves may also develop in other areas of the vertebral column to help maintain the head positioned over the feet. Scoliosis is the most common vertebral abnormality among girls. The cause is usually unknown, but it may result from weakness of the back muscles, defects such as differential growth rates in the right and left sides of the vertebral column, or differences in the length of the lower limbs. When present, scoliosis tends to get worse during adolescent growth spurts. Although most individuals do not require treatment, a back brace may be recommended for growing children. In extreme cases, surgery may be required.

Excessive vertebral curves can be identified while an individual stands in the anatomical position. Observe the vertebral profile from the side and then from behind to check for kyphosis or lordosis. Then have the person bend forward. If scoliosis is present, an individual will have difficulty in bending directly forward, and the right and left sides of the back will not be level with each other in the bent position.



(a) Scoliosis (b) Kyphosis (c) Lordosis

FIGURE 7.21 Abnormal Curvatures of the Vertebral Column (a) Scoliosis is an abnormal lateral bending of the vertebral column. (b) An excessive curvature of the upper thoracic vertebral column is called kyphosis. (c) Lordosis is an excessive curvature in the

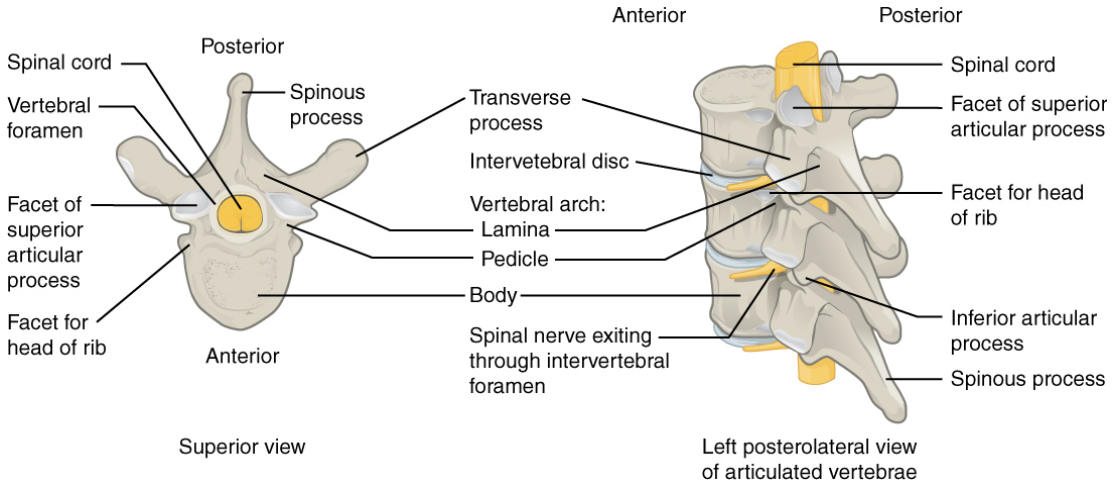


FIGURE 7.23 Parts of a Typical Vertebra A typical vertebra consists of a body and a vertebral arch. The arch is formed by the paired pedicles and paired laminae. Arising from the vertebral arch are the transverse, spinous, superior articular, and inferior articular processes. The vertebral foramen provides for passage of the spinal cord. Each spinal nerve exits through an intervertebral foramen, located between adjacent vertebrae. Intervertebral discs unite the bodies of adjacent vertebrae.

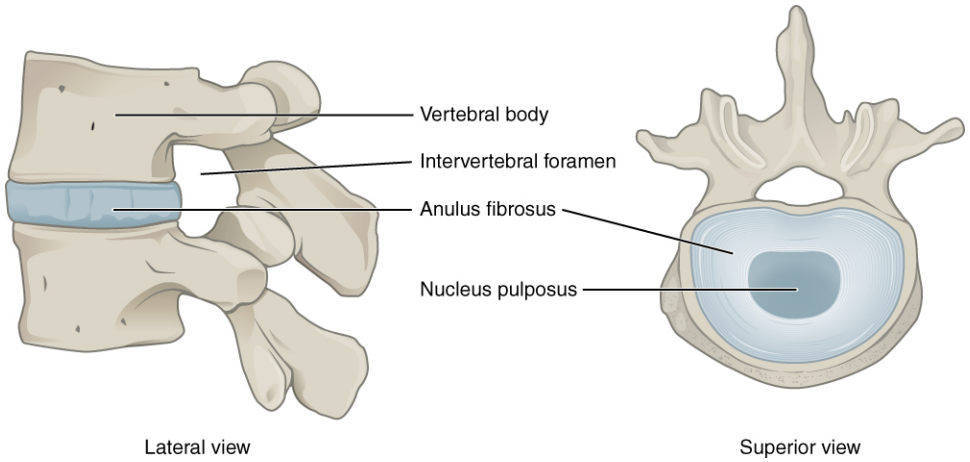


FIGURE 7.24 Intervertebral Disc The bodies of adjacent vertebrae are separated and united by an intervertebral disc, which provides padding and allows for movements between adjacent vertebrae. The disc consists of a fibrous outer layer called the anulus fibrosus and a gel-like center called the nucleus pulposus. The intervertebral foramen is the opening formed between adjacent vertebrae for the exit of a spinal nerve.

Regional Modifications of Vertebrae

In addition to the general characteristics of a typical vertebra described above, vertebrae also display characteristic size and structural features that vary between the different vertebral column regions. Thus, cervical vertebrae are smaller than lumbar vertebrae due to differences in the proportion of body weight that each supports. Thoracic vertebrae have sites for rib attachment, and the vertebrae that give rise to the sacrum and coccyx have fused together into single bones.

Cervical Vertebrae

Typical **cervical vertebrae**, such as C4 or C5, have several characteristic features that differentiate them from thoracic or lumbar vertebrae (Figure 7.25). Cervical vertebrae have a small body, reflecting the fact that they carry the least amount of body weight. Cervical vertebrae usually have a bifid (Y-shaped) spinous process. The spinous processes of the C3–C6 vertebrae are short, but the spine of C7 is much longer. You can find these vertebrae by running your finger down the midline of the posterior neck until you encounter the prominent C7 spine located at the base of the neck. The transverse processes of the cervical vertebrae are sharply curved (U-shaped) to allow for passage of the cervical spinal nerves. Each transverse process also has an opening called the **transverse foramen**. An important artery that supplies the brain ascends up the neck by passing through these openings. The superior and inferior articular processes of the cervical vertebrae are flattened and largely face upward or downward, respectively.

Thoracic Vertebrae

The bodies of the **thoracic vertebrae** are larger than those of cervical vertebrae (Figure 7.26). The characteristic feature for a typical midthoracic vertebra is the spinous process, which is long and has a pronounced downward angle that causes it to overlap the next inferior vertebra. The superior articular processes of thoracic vertebrae face anteriorly and the inferior processes face posteriorly. These orientations are important determinants for the type and range of movements available to the thoracic region of the vertebral column.

Thoracic vertebrae have several additional articulation sites, each of which is called a **facet**, where a rib is attached. Most thoracic vertebrae have two facets located on the lateral sides of the body, each of which is called a **costal facet** (costal = "rib"). These are for articulation with the head (end) of a rib. An additional facet is located on the transverse process for articulation with the tubercle of a rib.

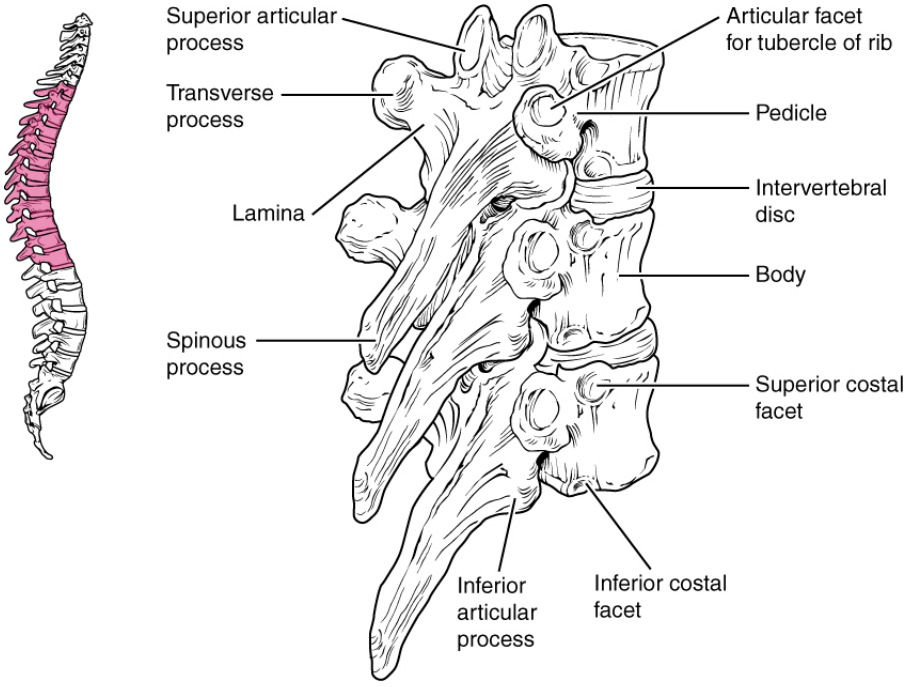


FIGURE 7.26 Thoracic Vertebrae A typical thoracic vertebra is distinguished by the spinous process, which is long and projects downward to overlap the next inferior vertebra. It also has articulation sites (facets) on the vertebral body and a transverse process for rib attachment.

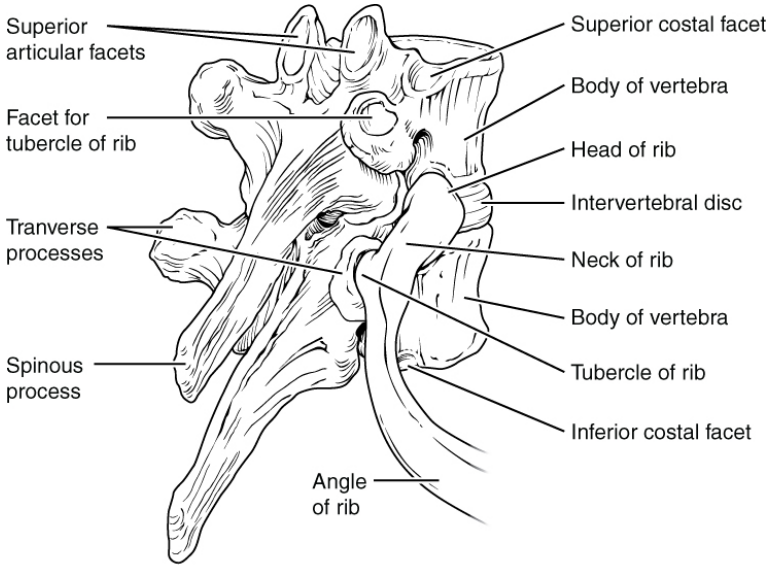


FIGURE 7.27 Rib Articulation in Thoracic Vertebrae Thoracic vertebrae have superior and inferior articular facets on the vertebral body for articulation with the head of a rib, and a transverse process facet for articulation with the rib tubercle.

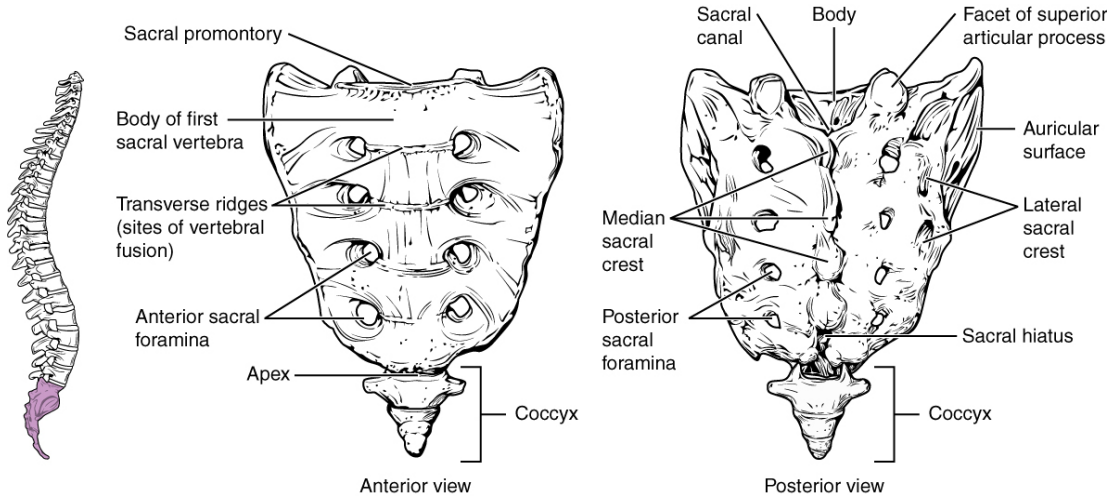


FIGURE 7.29 Sacrum and Coccyx The sacrum is formed from the fusion of five sacral vertebrae, whose lines of fusion are indicated by the transverse ridges. The fused spinous processes form the median sacral crest, while the lateral sacral crest arises from the fused transverse processes. The coccyx is formed by the fusion of four small coccygeal vertebrae.

Intervertebral Discs and Ligaments of the Vertebral Column

The bodies of adjacent vertebrae are strongly anchored to each other by an intervertebral disc. This structure provides padding between the bones during weight bearing, and because it can change shape, also allows for movement between the vertebrae. Although the total amount of movement available between any two adjacent vertebrae is small, when these movements are summed together along the entire length of the vertebral column, large body movements can be produced. Ligaments that extend along the length of the vertebral column also contribute to its overall support and stability.

Intervertebral Disc

An **intervertebral disc** is a fibrocartilaginous pad that fills the gap between adjacent vertebral bodies (see Figure 7.24). Each disc is anchored to the bodies of its adjacent vertebrae, thus strongly uniting these. The discs also provide padding between vertebrae during weight bearing. Because of this, intervertebral discs are thin in the cervical region and thickest in the lumbar region, which carries the most body weight. In total, the intervertebral discs account for approximately 25 percent of your body height between the top of the pelvis and the base of the skull. Intervertebral discs are also flexible and can change shape to allow for movements of the vertebral column.

Each intervertebral disc consists of two parts. The **anulus fibrosus** is the tough, fibrous outer layer of the disc. It forms a circle (anulus = “ring” or “circle”) and is firmly anchored to the outer margins of the adjacent vertebral bodies. Inside is the **nucleus pulposus**, consisting of a softer, more gel-like material. It has a high water content that serves to resist compression and thus is important for weight bearing. With increasing age, the water content of the nucleus pulposus gradually declines. This causes the disc to become thinner, decreasing total body height somewhat, and reduces the flexibility and range of motion of the disc, making bending more difficult.

The gel-like nature of the nucleus pulposus also allows the intervertebral disc to change shape as one vertebra rocks side to side or forward and back in relation to its neighbors during movements of the vertebral column. Thus, bending forward causes compression of the anterior portion of the disc but expansion of the posterior disc. If the posterior anulus fibrosus is weakened due to injury or increasing age, the pressure exerted on the disc when bending forward and lifting a heavy object can cause the nucleus pulposus to protrude posteriorly through the anulus fibrosus, resulting in a herniated disc (“ruptured” or “slipped” disc) (Figure 7.30). The posterior bulging of the nucleus pulposus can cause compression of a spinal nerve at the point where it exits through the intervertebral foramen, with resulting pain and/or muscle weakness in those body regions supplied by that nerve. The most common sites for disc herniation are the L4/L5 or L5/S1 intervertebral discs, which can cause sciatica, a widespread pain that radiates from the lower back down the thigh and into the leg. Similar injuries of the C5/C6 or C6/C7 intervertebral discs, following forcible hyperflexion of the neck from a collision accident or football injury, can produce pain in the neck, shoulder, and upper limb.

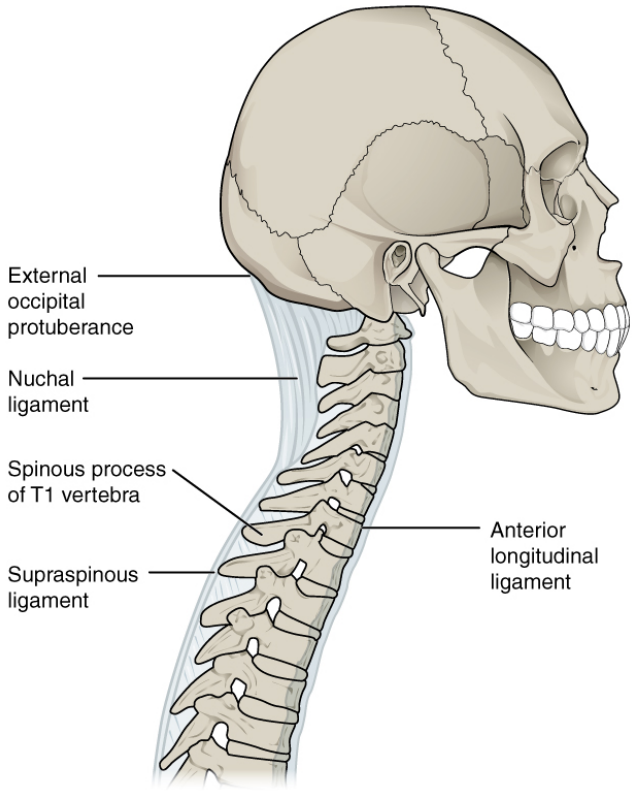


FIGURE 7.31 Ligaments of Vertebral Column The anterior longitudinal ligament runs the length of the vertebral column, uniting the anterior sides of the vertebral bodies. The supraspinous ligament connects the spinous processes of the thoracic and lumbar vertebrae. In the posterior neck, the supraspinous ligament enlarges to form the nuchal ligament, which attaches to the cervical spinous processes and to the base of the skull.

INTERACTIVE LINK

Use this tool (http://openstax.org/l/vertcolumn) to identify the bones, intervertebral discs, and ligaments of the vertebral column. The thickest portions of the anterior longitudinal ligament and the supraspinous ligament are found in which regions of the vertebral column?

CAREER CONNECTION

Chiropractor

Chiropractors are health professionals who use nonsurgical techniques to help patients with musculoskeletal system problems that involve the bones, muscles, ligaments, tendons, or nervous system. They treat problems such as neck pain, back pain, joint pain, or headaches. Chiropractors focus on the patient's overall health and can also provide counseling related to lifestyle issues, such as diet, exercise, or sleep problems. If needed, they will refer the patient to other medical specialists.

Chiropractors use a drug-free, hands-on approach for patient diagnosis and treatment. They will perform a physical exam, assess the patient's posture and spine, and may perform additional diagnostic tests, including taking X-ray images. They primarily use manual techniques, such as spinal manipulation, to adjust the patient's spine or other joints. They can recommend therapeutic or rehabilitative exercises, and some also include acupuncture, massage therapy, or ultrasound as part of the treatment program. In addition to those in general practice, some chiropractors specialize in sport injuries, neurology, orthopaedics, pediatrics, nutrition, internal disorders, or diagnostic imaging.

To become a chiropractor, students must have 3–4 years of undergraduate education, attend an accredited, four-year Doctor of Chiropractic (D.C.) degree program, and pass a licensure examination to be licensed for practice in their state. With the aging of the baby-boom generation, employment for chiropractors is expected to increase.

of ribs. The ribs are numbered 1–12 in accordance with the thoracic vertebrae.

Parts of a Typical Rib

The posterior end of a typical rib is called the **head of the rib** (see Figure 7.27). This region articulates primarily with the costal facet located on the body of the same numbered thoracic vertebra and to a lesser degree, with the costal facet located on the body of the next higher vertebra. Lateral to the head is the narrowed **neck of the rib**. A small bump on the posterior rib surface is the **tubercle of the rib**, which articulates with the facet located on the transverse process of the same numbered vertebra. The remainder of the rib is the **body of the rib** (shaft). Just lateral to the tubercle is the **angle of the rib**, the point at which the rib has its greatest degree of curvature. The angles of the ribs form the most posterior extent of the thoracic cage. In the anatomical position, the angles align with the medial border of the scapula. A shallow **costal groove** for the passage of blood vessels and a nerve is found along the inferior margin of each rib.

Rib Classifications

The bony ribs do not extend anteriorly completely around to the sternum. Instead, each rib ends in a **costal cartilage**. These cartilages are made of hyaline cartilage and can extend for several inches. Most ribs are then attached, either directly or indirectly, to the sternum via their costal cartilage (see Figure 7.32). The ribs are classified into three groups based on their relationship to the sternum.

Ribs 1–7 are classified as **true ribs** (vertebrosternal ribs). The costal cartilage from each of these ribs attaches directly to the sternum. Ribs 8–12 are called **false ribs** (vertebrochondral ribs). The costal cartilages from these ribs do not attach directly to the sternum. For ribs 8–10, the costal cartilages are attached to the cartilage of the next higher rib. Thus, the cartilage of rib 10 attaches to the cartilage of rib 9, rib 9 then attaches to rib 8, and rib 8 is attached to rib 7. The last two false ribs (11–12) are also called **floating ribs** (vertebral ribs). These are short ribs that do not attach to the sternum at all. Instead, their small costal cartilages terminate within the musculature of the lateral abdominal wall.

7.5 Embryonic Development of the Axial Skeleton

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the two types of embryonic bone development within the skull
- Describe the development of the vertebral column and thoracic cage

The axial skeleton begins to form during early embryonic development. However, growth, remodeling, and ossification (bone formation) continue for several decades after birth before the adult skeleton is fully formed. Knowledge of the developmental processes that give rise to the skeleton is important for understanding the abnormalities that may arise in skeletal structures.

Development of the Skull

During the third week of embryonic development, a rod-like structure called the **notochord** develops dorsally along the length of the embryo. The tissue overlying the notochord enlarges and forms the neural tube, which will give rise to the brain and spinal cord. By the fourth week, mesoderm tissue located on either side of the notochord thickens and separates into a repeating series of block-like tissue structures, each of which is called a **somite**. As the somites enlarge, each one will split into several parts. The most medial of these parts is called a **sclerotome**. The sclerotomes consist of an embryonic tissue called mesenchyme, which will give rise to the fibrous connective tissues, cartilages, and bones of the body.

The bones of the skull arise from mesenchyme during embryonic development in two different ways. The first mechanism produces the bones that form the top and sides of the brain case. This involves the local accumulation of mesenchymal cells at the site of the future bone. These cells then differentiate directly into bone producing cells, which form the skull bones through the process of intramembranous ossification. As the brain case bones grow in the fetal skull, they remain separated from each other by large areas of dense connective tissue, each of which is called a **fontanelle** (Figure 7.33). The fontanelles are the soft spots on an infant's head. They are important during birth because these areas allow the skull to change shape as it squeezes through the birth canal. After birth, the fontanelles allow for continued growth and expansion of the skull as the brain enlarges. The largest fontanelle is

HOMEOSTATIC IMBALANCES

Craniosynostosis

The premature closure (fusion) of a suture line is a condition called craniosynostosis. This error in the normal developmental process results in abnormal growth of the skull and deformity of the head. It is produced either by defects in the ossification process of the skull bones or failure of the brain to properly enlarge. Genetic factors are involved, but the underlying cause is unknown. It is a relatively common condition, occurring in approximately 1:2000 births, with males being more commonly affected. Primary craniosynostosis involves the early fusion of one cranial suture, whereas complex craniosynostosis results from the premature fusion of several sutures.

The early fusion of a suture in primary craniosynostosis prevents any additional enlargement of the cranial bones and skull along this line. Continued growth of the brain and skull is therefore diverted to other areas of the head, causing an abnormal enlargement of these regions. For example, the early disappearance of the anterior fontanelle and premature closure of the sagittal suture prevents growth across the top of the head. This is compensated by upward growth by the bones of the lateral skull, resulting in a long, narrow, wedge-shaped head. This condition, known as scaphocephaly, accounts for approximately 50 percent of craniosynostosis abnormalities. Although the skull is misshapen, the brain still has adequate room to grow and thus there is no accompanying abnormal neurological development.

In cases of complex craniosynostosis, several sutures close prematurely. The amount and degree of skull deformity is determined by the location and extent of the sutures involved. This results in more severe constraints on skull growth, which can alter or impede proper brain growth and development.

Cases of craniosynostosis are usually treated with surgery. A team of physicians will open the skull along the fused suture, which will then allow the skull bones to resume their growth in this area. In some cases, parts of the skull will be removed and replaced with an artificial plate. The earlier after birth that surgery is performed, the better the outcome. After treatment, most children continue to grow and develop normally and do not exhibit any neurological problems.

on the lateral side of the skull

external occipital protuberance small bump located at the midline on the posterior skull

facet small, flattened area on a bone for an articulation (joint) with another bone, or for muscle attachment

facial bones fourteen bones that support the facial structures and form the upper and lower jaws and the hard palate

false ribs vertebrochondral ribs 8–12 whose costal cartilage either attaches indirectly to the sternum via the costal cartilage of the next higher rib or does not attach to the sternum at all

floating ribs vertebral ribs 11–12 that do not attach to the sternum or to the costal cartilage of another rib

fontanelle expanded area of fibrous connective tissue that separates the brain case bones of the skull prior to birth and during the first year after birth

foramen lacerum irregular opening in the base of the skull, located inferior to the exit of carotid canal

foramen magnum large opening in the occipital bone of the skull through which the spinal cord emerges and the vertebral arteries enter the cranium

foramen ovale of the middle cranial fossa oval-shaped opening in the floor of the middle cranial fossa

foramen rotundum round opening in the floor of the middle cranial fossa, located between the superior orbital fissure and foramen ovale

foramen spinosum small opening in the floor of the middle cranial fossa, located lateral to the foramen ovale

frontal bone unpaired bone that forms forehead, roof of orbit, and floor of anterior cranial fossa

frontal sinus air-filled space within the frontal bone; most anterior of the paranasal sinuses

glabella slight depression of frontal bone, located at the midline between the eyebrows

greater wings of sphenoid bone lateral projections of the sphenoid bone that form the anterior wall of the middle cranial fossa and an area of the lateral skull

hard palate bony structure that forms the roof of the mouth and floor of the nasal cavity, formed by the palatine process of the maxillary bones and the horizontal plate of the palatine bones

head of the rib posterior end of a rib that articulates with the bodies of thoracic vertebrae

horizontal plate medial extension from the palatine bone that forms the posterior quarter of the hard palate

hyoid bone small, U-shaped bone located in upper neck that does not contact any other bone

hypoglossal canal paired openings that pass anteriorly from the anterior-lateral margins of the foramen magnum deep to the occipital condyles

hypophyseal (pituitary) fossa shallow depression on top of the sella turcica that houses the pituitary (hypophyseal) gland

inferior articular process bony process that extends downward from the vertebral arch of a vertebra that articulates with the superior articular process of the next lower vertebra

inferior nasal concha one of the paired bones that project from the lateral walls of the nasal cavity to form the largest and most inferior of the nasal conchae

infraorbital foramen opening located on anterior skull, below the orbit

infratemporal fossa space on lateral side of skull, below the level of the zygomatic arch and deep (medial) to the ramus of the mandible

internal acoustic meatus opening into petrous ridge, located on the lateral wall of the posterior cranial fossa

intervertebral disc structure located between the bodies of adjacent vertebrae that strongly joins the vertebrae; provides padding, weight bearing ability, and enables vertebral column movements

intervertebral foramen opening located between adjacent vertebrae for exit of a spinal nerve

jugular (suprasternal) notch shallow notch located on superior surface of sternal manubrium

jugular foramen irregularly shaped opening located in the lateral floor of the posterior cranial cavity

kyphosis (also, humpback or hunchback) excessive posterior curvature of the thoracic vertebral column region

lacrimal bone paired bones that contribute to the anterior-medial wall of each orbit

lacrimal fossa shallow depression in the anterior-medial wall of the orbit, formed by the lacrimal bone that gives rise to the nasolacrimal canal

lambdoid suture inverted V-shaped joint that unites the occipital bone to the right and left parietal bones on the posterior skull

lamina portion of the vertebral arch on each vertebra that extends between the transverse and spinous process

lateral pterygoid plate paired, flattened bony projections of the sphenoid bone located on the inferior skull, lateral to the medial pterygoid plate

lateral sacral crest paired irregular ridges running down the lateral sides of the posterior sacrum that

parietal bone paired bones that form the upper, lateral sides of the skull

pedicle portion of the vertebral arch that extends from the vertebral body to the transverse process

perpendicular plate of the ethmoid bone downward, midline extension of the ethmoid bone that forms the superior portion of the nasal septum

petrous ridge petrous portion of the temporal bone that forms a large, triangular ridge in the floor of the cranial cavity, separating the middle and posterior cranial fossae; houses the middle and inner ear structures

posterior (dorsal) sacral foramen one of the series of paired openings located on the posterior (dorsal) side of the sacrum

posterior arch posterior portion of the ring-like C1 (atlas) vertebra

posterior cranial fossa deepest and most posterior cranial fossa; extends from the petrous ridge to the occipital bone

posterior longitudinal ligament ligament that runs the length of the vertebral column, uniting the posterior sides of the vertebral bodies

primary curve anteriorly concave curvatures of the thoracic and sacrococcygeal regions that are retained from the original fetal curvature of the vertebral column

pterion H-shaped suture junction region that unites the frontal, parietal, temporal, and sphenoid bones on the lateral side of the skull

ramus of the mandible vertical portion of the mandible

ribs thin, curved bones of the chest wall

sacral canal bony tunnel that runs through the sacrum

sacral foramina series of paired openings for nerve exit located on both the anterior (ventral) and posterior (dorsal) aspects of the sacrum

sacral hiatus inferior opening and termination of the sacral canal

sacral promontory anterior lip of the base (superior end) of the sacrum

sacrococcygeal curve anteriorly concave curvature formed by the sacrum and coccyx; a primary curve of the vertebral column

sacrum single bone located near the inferior end of the adult vertebral column that is formed by the fusion of five sacral vertebrae; forms the posterior portion of the pelvis

sagittal suture joint that unites the right and left parietal bones at the midline along the top of the skull

sclerotome medial portion of a somite consisting of mesenchyme tissue that will give rise to bone, cartilage, and fibrous connective tissues

scoliosis abnormal lateral curvature of the vertebral column

secondary curve posteriorly concave curvatures of the cervical and lumbar regions of the vertebral column that develop after the time of birth

sella turcica elevated area of sphenoid bone located at midline of the middle cranial fossa

septal cartilage flat cartilage structure that forms the anterior portion of the nasal septum

skeleton bones of the body

skull bony structure that forms the head, face, and jaws, and protects the brain; consists of 22 bones

somite one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

sphenoid bone unpaired bone that forms the central base of skull

sphenoid sinus air-filled space located within the sphenoid bone; most posterior of the paranasal sinuses

spinous process unpaired bony process that extends posteriorly from the vertebral arch of a vertebra

squamous suture joint that unites the parietal bone to the squamous portion of the temporal bone on the lateral side of the skull

sternal angle junction line between manubrium and body of the sternum and the site for attachment of the second rib to the sternum

sternum flattened bone located at the center of the anterior chest

styloid process downward projecting, elongated bony process located on the inferior aspect of the skull

stylomastoid foramen opening located on inferior skull, between the styloid process and mastoid process

superior articular process bony process that extends upward from the vertebral arch of a vertebra that articulates with the inferior articular process of the next higher vertebra

superior articular process of the sacrum paired processes that extend upward from the sacrum to articulate (join) with the inferior articular processes from the L5 vertebra

superior nasal concha smallest and most superiorly located of the nasal conchae; formed by the ethmoid bone

superior nuchal line paired bony lines on the posterior skull that extend laterally from the external occipital protuberance

superior orbital fissure irregularly shaped opening

vomer and mandible bones. The ethmoid bone also contributes to the formation of facial structures. The maxilla forms the upper jaw and the mandible forms the lower jaw. The maxilla also forms the larger anterior portion of the hard palate, which is completed by the smaller palatine bones that form the posterior portion of the hard palate.

The floor of the cranial cavity increases in depth from front to back and is divided into three cranial fossae. The anterior cranial fossa is located between the frontal bone and lesser wing of the sphenoid bone. A small area of the ethmoid bone, consisting of the crista galli and cribriform plates, is located at the midline of this fossa. The middle cranial fossa extends from the lesser wing of the sphenoid bone to the petrous ridge (petrous portion of temporal bone). The right and left sides are separated at the midline by the sella turcica, which surrounds the shallow hypophyseal fossa. Openings through the skull in the floor of the middle fossa include the optic canal and superior orbital fissure, which open into the posterior orbit, the foramen rotundum, foramen ovale, and foramen spinosum, and the exit of the carotid canal with its underlying foramen lacerum. The deep posterior cranial fossa extends from the petrous ridge to the occipital bone. Openings here include the large foramen magnum, plus the internal acoustic meatus, jugular foramina, and hypoglossal canals. Additional openings located on the external base of the skull include the stylomastoid foramen and the entrance to the carotid canal.

The anterior skull has the orbits that house the eyeballs and associated muscles. The walls of the orbit are formed by contributions from seven bones: the frontal, zygomatic, maxillary, palatine, ethmoid, lacrimal, and sphenoid. Located at the superior margin of the orbit is the supraorbital foramen, and below the orbit is the infraorbital foramen. The mandible has two openings, the mandibular foramen on its inner surface and the mental foramen on its external surface near the chin. The nasal conchae are bony projections from the lateral walls of the nasal cavity. The large inferior nasal concha is an independent bone, while the middle and superior conchae are parts of the ethmoid bone. The nasal septum is formed by the perpendicular plate of the ethmoid bone, the vomer bone, and the septal cartilage. The paranasal sinuses are air-filled spaces located within the frontal, maxillary, sphenoid, and ethmoid bones.

On the lateral skull, the zygomatic arch consists of two parts, the temporal process of the zygomatic bone anteriorly and the zygomatic process of the temporal bone posteriorly. The temporal fossa is the shallow space located on the lateral skull above the level of the zygomatic arch. The infratemporal fossa is located below the zygomatic arch and deep to the ramus of the mandible.

The hyoid bone is located in the upper neck and does not join with any other bone. It is held in position by muscles and serves to support the tongue above, the larynx below, and the pharynx posteriorly.

7.3 The Vertebral Column

The vertebral column forms the neck and back. The vertebral column originally develops as 33 vertebrae, but is eventually reduced to 24 vertebrae, plus the sacrum and coccyx. The vertebrae are divided into the cervical region (C1–C7 vertebrae), the thoracic region (T1–T12 vertebrae), and the lumbar region (L1–L5 vertebrae). The sacrum arises from the fusion of five sacral vertebrae and the coccyx from the fusion of four small coccygeal vertebrae. The vertebral column has four curvatures, the cervical, thoracic, lumbar, and sacrococcygeal curves. The thoracic and sacrococcygeal curves are primary curves retained from the original fetal curvature. The cervical and lumbar curves develop after birth and thus are secondary curves. The cervical curve develops as the infant begins to hold up the head, and the lumbar curve appears with standing and walking.

A typical vertebra consists of an enlarged anterior portion called the body, which provides weight-bearing support. Attached posteriorly to the body is a vertebral arch, which surrounds and defines the vertebral foramen for passage of the spinal cord. The vertebral arch consists of the pedicles, which attach to the vertebral body, and the laminae, which come together to form the roof of the arch. Arising from the vertebral arch are the laterally projecting transverse processes and the posteriorly oriented spinous process. The superior articular processes project upward, where they articulate with the downward projecting inferior articular processes of the next higher vertebrae.

A typical cervical vertebra has a small body, a bifid (Y-shaped) spinous process, and U-shaped transverse processes with a transverse foramen. In addition to these characteristics, the axis (C2 vertebra) also has the dens projecting upward from the vertebral body. The atlas (C1 vertebra) differs from the other cervical vertebrae in that it does not have a body, but instead consists of bony ring formed by the anterior and posterior arches. The atlas articulates with the dens from the axis. A typical thoracic vertebra is distinguished by its long, downward projecting spinous

Interactive Link Questions

1. Watch this video (http://openstax.org/l/skull1) to view a rotating and exploded skull with color-coded bones. Which bone (yellow) is centrally located and joins with most of the other bones of the skull?
2. View this animation (http://openstax.org/l/headblow) to see how a blow to the head may produce a contrecoup (counterblow) fracture of the basilar portion of the occipital bone on the base of the skull. Why may a basilar fracture be life threatening?
3. Osteoporosis is a common age-related bone disease in which bone density and strength is decreased. Watch this video (http://openstax.org/l/osteoporosis) to get a better understanding of how thoracic vertebrae may become weakened and may fractured due to this disease. How may vertebral osteoporosis contribute to kyphosis?
4. Watch this video (http://openstax.org/l/herndisc1) to learn about a herniated disc. Watch this second video (http://openstax.org/l/herndisc2) to see one possible treatment for a herniated disc, removing the damaged portion of the disc. How could lifting a heavy object produce pain in a lower limb?
5. Use this tool (http://openstax.org/l/vertcolumn) to identify the bones, intervertebral discs, and ligaments of the vertebral column. The thickest portions of the anterior longitudinal ligament and the supraspinous ligament are found in which regions of the vertebral column?
6. View this video (http://openstax.org/l/skullbones) to review the two processes that give rise to the bones of the skull and body. What are the two mechanisms by which the bones of the body are formed and which bones are formed by each mechanism?

Review Questions

7. Which of the following is part of the axial skeleton?
   a. shoulder bones
   b. thigh bone
   c. foot bones
   d. vertebral column

8. Which of the following is a function of the axial skeleton?
   a. allows for movement of the wrist and hand
   b. protects nerves and blood vessels at the elbow
   c. supports trunk of body
   d. allows for movements of the ankle and foot

9. The axial skeleton _____.
   a. consists of 126 bones
   b. forms the vertical axis of the body
   c. includes all bones of the body trunk and limbs
   d. includes only the bones of the lower limbs

10. Which of the following is a bone of the brain case?
    a. parietal bone
    b. zygomatic bone
    c. maxillary bone
    d. lacrimal bone

11. The lambdoid suture joins the parietal bone to the _____.
    a. frontal bone
    b. occipital bone
    c. other parietal bone
    d. temporal bone

12. The middle cranial fossa _____.
    a. is bounded anteriorly by the petrous ridge
    b. is bounded posteriorly by the lesser wing of the sphenoid bone
    c. is divided at the midline by a small area of the ethmoid bone
    d. has the foramen rotundum, foramen ovale, and foramen spinosum

13. The paranasal sinuses are _____.
    a. air-filled spaces found within the frontal, maxilla, sphenoid, and ethmoid bones only
    b. air-filled spaces found within all bones of the skull
    c. not connected to the nasal cavity
    d. divided at the midline by the nasal septum

14. Parts of the sphenoid bone include the _____.
    a. sella turcica
    b. squamous portion
    c. glabella
    d. zygomatic process

15. The bony openings of the skull include the _____.
    a. carotid canal, which is located in the anterior cranial fossa
    b. superior orbital fissure, which is located at the superior margin of the anterior orbit
    c. mental foramen, which is located just below the orbit
    d. hypoglossal canal, which is located in the posterior cranial fossa

31. Describe the anterior, middle, and posterior cranial fossae and their boundaries, and give the midline structure that divides each into right and left areas.
32. Describe the parts of the nasal septum in both the dry and living skull.
33. Describe the vertebral column and define each region.
34. Describe a typical vertebra.
35. Describe the sacrum.
36. Describe the structure and function of an intervertebral disc.
37. Define the ligaments of the vertebral column.
38. Define the parts and functions of the thoracic cage.
39. Describe the parts of the sternum.
40. Discuss the parts of a typical rib.
41. Define the classes of ribs.
42. Discuss the processes by which the brain-case bones of the skull are formed and grow during skull enlargement.
43. Discuss the process that gives rise to the base and facial bones of the skull.
44. Discuss the development of the vertebrae, ribs, and sternum.

(Figure 8.2). The bones that attach each upper limb to the axial skeleton form the pectoral girdle (shoulder girdle). This consists of two bones, the scapula and clavicle (Figure 8.3). The clavicle (collarbone) is an S-shaped bone located on the anterior side of the shoulder. It is attached on its medial end to the sternum of the thoracic cage, which is part of the axial skeleton. The lateral end of the clavicle articulates (joins) with the scapula just above the shoulder joint. You can easily palpate, or feel with your fingers, the entire length of your clavicle.

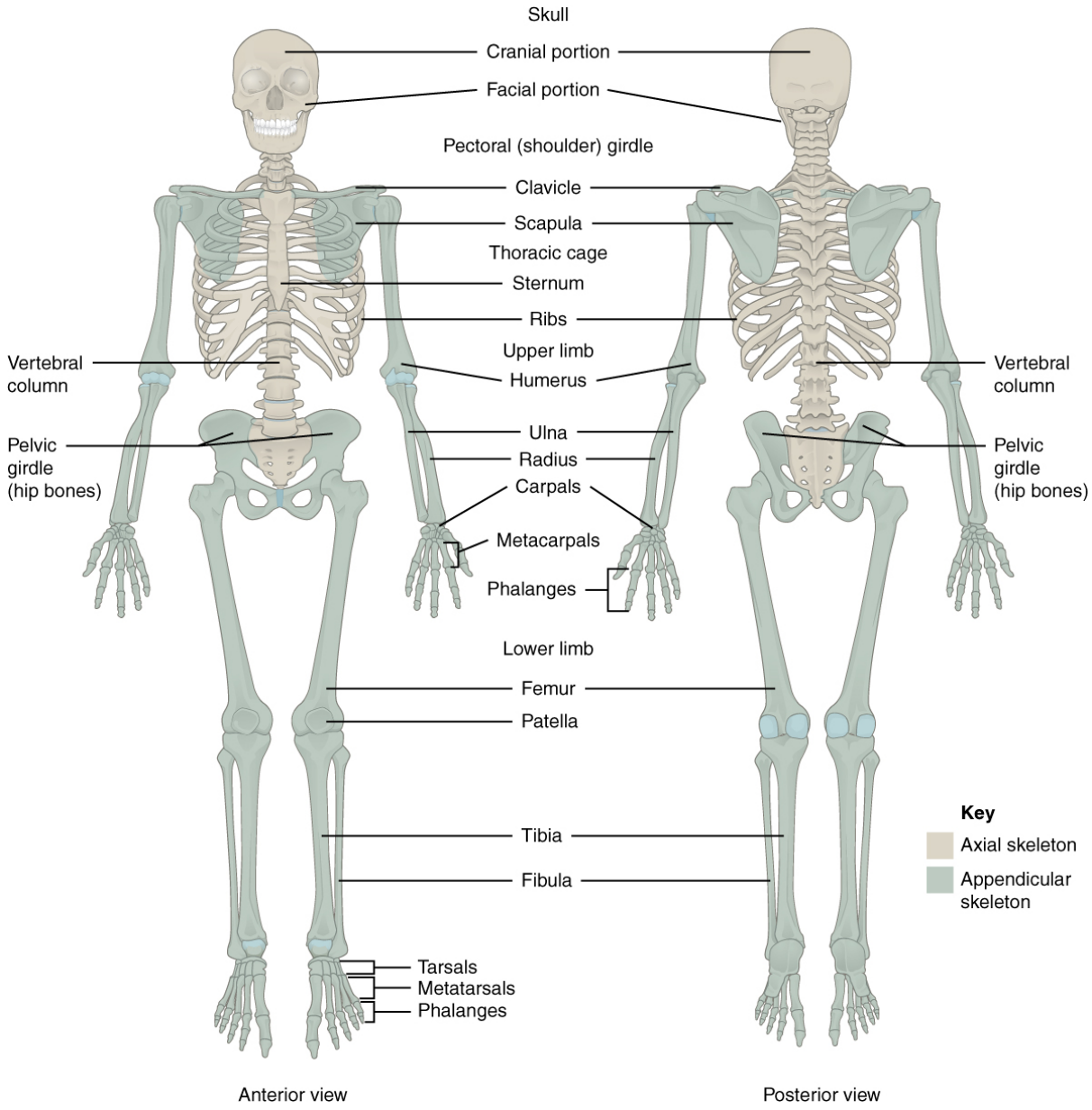


FIGURE 8.2 Axial and Appendicular Skeletons The axial skeleton forms the central axis of the body and consists of the skull, vertebral column, and thoracic cage. The appendicular skeleton consists of the pectoral and pelvic girdles, the limb bones, and the bones of the hands and feet.

several important functions. First, anchored by muscles from above, it serves as a strut that extends laterally to support the scapula. This in turn holds the shoulder joint superiorly and laterally from the body trunk, allowing for maximal freedom of motion for the upper limb. The clavicle also transmits forces acting on the upper limb to the sternum and axial skeleton. Finally, it serves to protect the underlying nerves and blood vessels as they pass between the trunk of the body and the upper limb.

The clavicle has three regions: the medial end, the lateral end, and the shaft. The medial end, known as the **sternal end of the clavicle**, has a triangular shape and articulates with the manubrium portion of the sternum. This forms the **sternoclavicular joint**, which is the only bony articulation between the pectoral girdle of the upper limb and the axial skeleton. This joint allows considerable mobility, enabling the clavicle and scapula to move in upward/downward and anterior/posterior directions during shoulder movements. The sternoclavicular joint is indirectly supported by the **costoclavicular ligament** (costo- = "rib"), which spans the sternal end of the clavicle and the underlying first rib. The lateral or **acromial end of the clavicle** articulates with the acromion of the scapula, the portion of the scapula that forms the bony tip of the shoulder. There are some sex differences in the morphology of the clavicle. In females, the clavicle tends to be shorter, thinner, and less curved. In males, the clavicle is heavier and longer, and has a greater curvature and rougher surfaces where muscles attach, features that are more pronounced in manual workers.

The clavicle is the most commonly fractured bone in the body. Such breaks often occur because of the force exerted on the clavicle when a person falls onto their outstretched arms, or when the lateral shoulder receives a strong blow. Because the sternoclavicular joint is strong and rarely dislocated, excessive force results in the breaking of the clavicle, usually between the middle and lateral portions of the bone. If the fracture is complete, the shoulder and lateral clavicle fragment will drop due to the weight of the upper limb, causing the person to support the sagging limb with their other hand. Muscles acting across the shoulder will also pull the shoulder and lateral clavicle anteriorly and medially, causing the clavicle fragments to override. The clavicle overlies many important blood vessels and nerves for the upper limb, but fortunately, due to the anterior displacement of a broken clavicle, these structures are rarely affected when the clavicle is fractured.

Scapula

The scapula is also part of the pectoral girdle and thus plays an important role in anchoring the upper limb to the body. The scapula is located on the posterior side of the shoulder. It is surrounded by muscles on both its anterior (deep) and posterior (superficial) sides, and thus does not articulate with the ribs of the thoracic cage.

The scapula has several important landmarks (Figure 8.4). The three margins or borders of the scapula, named for their positions within the body, are the **superior border of the scapula**, the **medial border of the scapula**, and the **lateral border of the scapula**. The **suprascapular notch** is located lateral to the midpoint of the superior border. The corners of the triangular scapula, at either end of the medial border, are the **superior angle of the scapula**, located between the medial and superior borders, and the **inferior angle of the scapula**, located between the medial and lateral borders. The inferior angle is the most inferior portion of the scapula, and is particularly important because it serves as the attachment point for several powerful muscles involved in shoulder and upper limb movements. The remaining corner of the scapula, between the superior and lateral borders, is the location of the **glenoid cavity** (glenoid fossa). This shallow depression articulates with the humerus bone of the arm to form the **glenohumeral joint** (shoulder joint). The small bony bumps located immediately above and below the glenoid cavity are the **supraglenoid tubercle** and the **infraglenoid tubercle**, respectively. These provide attachments for muscles of the arm.

The upper limb is divided into three regions. These consist of the **arm**, located between the shoulder and elbow joints; the **forearm**, which is between the elbow and wrist joints; and the **hand**, which is located distal to the wrist. There are 30 bones in each upper limb (see Figure 8.2). The **humerus** is the single bone of the upper arm, and the **ulna** (medially) and the **radius** (laterally) are the paired bones of the forearm. The base of the hand contains eight bones, each called a **carpal bone**, and the palm of the hand is formed by five bones, each called a **metacarpal bone**. The fingers and thumb contain a total of 14 bones, each of which is a **phalanx bone of the hand**.

Humerus

The humerus is the single bone of the upper arm region (Figure 8.5). At its proximal end is the **head of the humerus**. This is the large, round, smooth region that faces medially. The head articulates with the glenoid cavity of the scapula to form the glenohumeral (shoulder) joint. The margin of the smooth area of the head is the **anatomical neck** of the humerus. Located on the lateral side of the proximal humerus is an expanded bony area called the **greater tubercle**. The smaller **lesser tubercle** of the humerus is found on the anterior aspect of the humerus. Both the greater and lesser tubercles serve as attachment sites for muscles that act across the shoulder joint. Passing between the greater and lesser tubercles is the narrow **intertubercular groove (sulcus)**, which is also known as the **bicipital groove** because it provides passage for a tendon of the biceps brachii muscle. The **surgical neck** is located at the base of the expanded, proximal end of the humerus, where it joins the narrow **shaft of the humerus**. The surgical neck is a common site of arm fractures. The **deltoid tuberosity** is a roughened, V-shaped region located on the lateral side in the middle of the humerus shaft. As its name indicates, it is the site of attachment for the deltoid muscle.

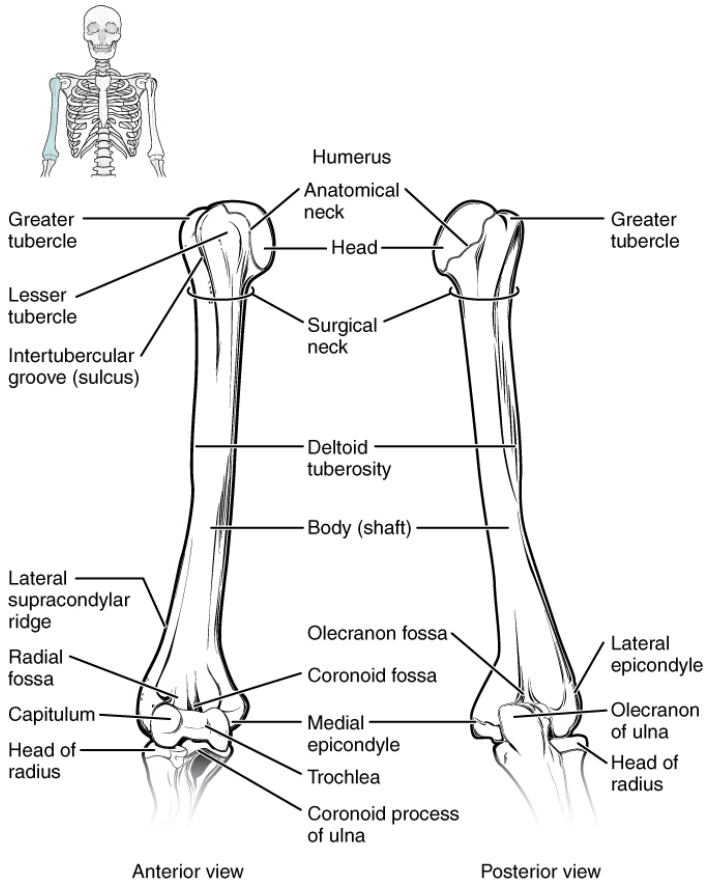


FIGURE 8.5 **Humerus and Elbow Joint** The humerus is the single bone of the upper arm region. It articulates with the radius and ulna bones of the forearm to form the elbow joint.

Distally, the humerus becomes flattened. The prominent bony projection on the medial side is the **medial epicondyle of the humerus**. The much smaller **lateral epicondyle of the humerus** is found on the lateral side of the distal humerus. The roughened ridge of bone above the lateral epicondyle is the **lateral supracondylar ridge**. All of these areas are attachment points for muscles that act on the forearm, wrist, and hand. The powerful grasping

ulna. This is the line of attachment for the **interosseous membrane of the forearm**, a sheet of dense connective tissue that unites the ulna and radius bones. The small, rounded area that forms the distal end is the **head of the ulna**. Projecting from the posterior side of the ulnar head is the **styloid process of the ulna**, a short bony projection. This serves as an attachment point for a connective tissue structure that unites the distal ends of the ulna and radius.

In the anatomical position, with the elbow fully extended and the palms facing forward, the arm and forearm do not form a straight line. Instead, the forearm deviates laterally by 5–15 degrees from the line of the arm. This deviation is called the carrying angle. It allows the forearm and hand to swing freely or to carry an object without hitting the hip. The carrying angle is larger in females to accommodate their wider pelvis.

Radius

The radius runs parallel to the ulna, on the lateral (thumb) side of the forearm (see Figure 8.6). The **head of the radius** is a disc-shaped structure that forms the proximal end. The small depression on the surface of the head articulates with the capitulum of the humerus as part of the elbow joint, whereas the smooth, outer margin of the head articulates with the radial notch of the ulna at the proximal radioulnar joint. The **neck of the radius** is the narrowed region immediately below the expanded head. Inferior to this point on the medial side is the **radial tuberosity**, an oval-shaped, bony protuberance that serves as a muscle attachment point. The **shaft of the radius** is slightly curved and has a small ridge along its medial side. This ridge forms the **interosseous border of the radius**, which, like the similar border of the ulna, is the line of attachment for the interosseous membrane that unites the two forearm bones. The distal end of the radius has a smooth surface for articulation with two carpal bones to form the **radiocarpal joint** or wrist joint (Figure 8.7 and Figure 8.8). On the medial side of the distal radius is the **ulnar notch of the radius**. This shallow depression articulates with the head of the ulna, which together form the **distal radioulnar joint**. The lateral end of the radius has a pointed projection called the **styloid process of the radius**. This provides attachment for ligaments that support the lateral side of the wrist joint. Compared to the styloid process of the ulna, the styloid process of the radius projects more distally, thereby limiting the range of movement for lateral deviations of the hand at the wrist joint.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/fractures) to see how fractures of the distal radius bone can affect the wrist joint. Explain the problems that may occur if a fracture of the distal radius involves the joint surface of the radiocarpal joint of the wrist.

Carpal Bones

The wrist and base of the hand are formed by a series of eight small carpal bones (see Figure 8.7). The carpal bones are arranged in two rows, forming a proximal row of four carpal bones and a distal row of four carpal bones. The bones in the proximal row, running from the lateral (thumb) side to the medial side, are the **scaphoid** (“boat-shaped”), **lunate** (“moon-shaped”), **triquetrum** (“three-cornered”), and **pisiform** (“pea-shaped”) bones. The small, rounded pisiform bone articulates with the anterior surface of the triquetrum bone. The pisiform thus projects anteriorly, where it forms the bony bump that can be felt at the medial base of your hand. The distal bones (lateral to medial) are the **trapezium** (“table”), **trapezoid** (“resembles a table”), **capitate** (“head-shaped”), and **hamate** (“hooked bone”) bones. The hamate bone is characterized by a prominent bony extension on its anterior side called the **hook of the hamate bone**.

A helpful mnemonic for remembering the arrangement of the carpal bones is “So Long To Pinky, Here Comes The Thumb.” This mnemonic starts on the lateral side and names the proximal bones from lateral to medial (scaphoid, lunate, triquetrum, pisiform), then makes a U-turn to name the distal bones from medial to lateral (hamate, capitate, trapezoid, trapezium). Thus, it starts and finishes on the lateral side.

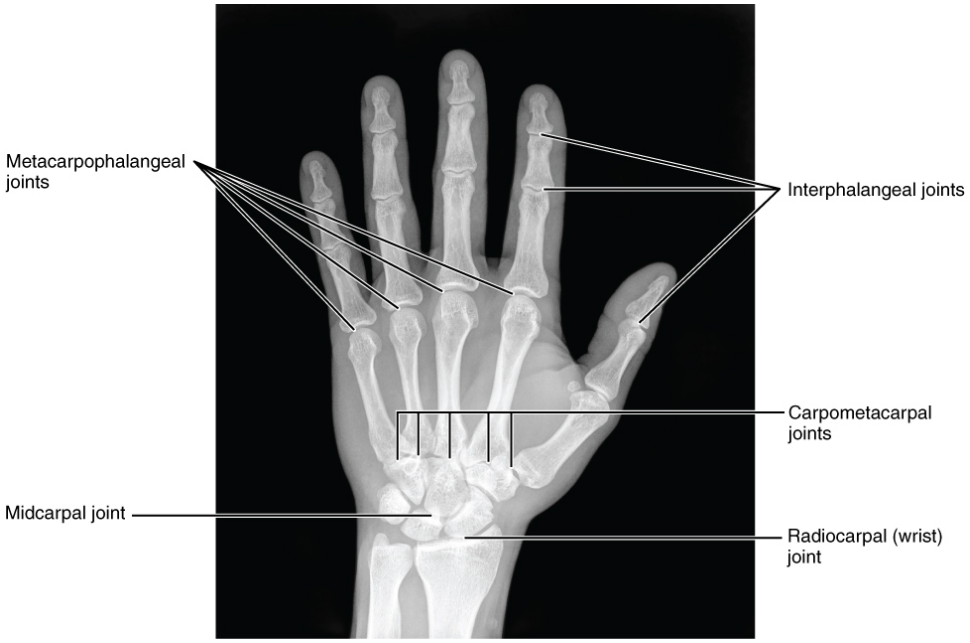


FIGURE 8.8 Bones of the Hand This radiograph shows the position of the bones within the hand. Note the carpal bones that form the base of the hand. (credit: modification of work by Trace Meek)

In the articulated hand, the carpal bones form a U-shaped grouping. A strong ligament called the **flexor retinaculum** spans the top of this U-shaped area to maintain this grouping of the carpal bones. The flexor retinaculum is attached laterally to the trapezium and scaphoid bones, and medially to the hamate and pisiform bones. Together, the carpal bones and the flexor retinaculum form a passageway called the **carpal tunnel**, with the carpal bones forming the walls and floor, and the flexor retinaculum forming the roof of this space (Figure 8.9). The tendons of nine muscles of the anterior forearm and an important nerve pass through this narrow tunnel to enter the hand. Overuse of the muscle tendons or wrist injury can produce inflammation and swelling within this space. This produces compression of the nerve, resulting in carpal tunnel syndrome, which is characterized by pain or numbness, and muscle weakness in those areas of the hand supplied by this nerve.

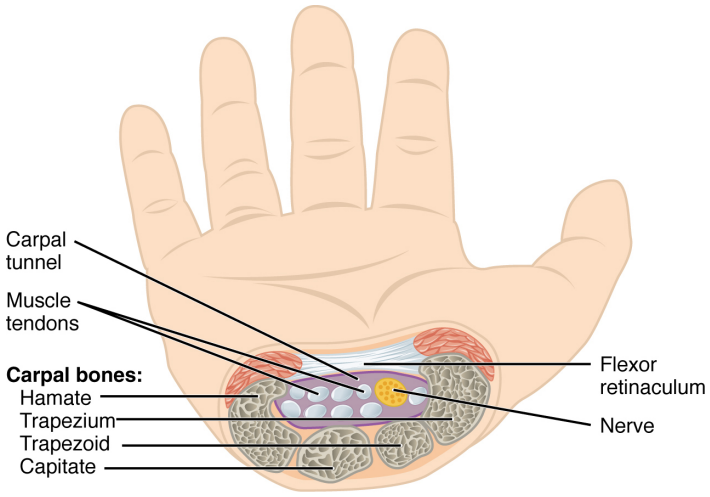


FIGURE 8.9 Carpal Tunnel The carpal tunnel is the passageway by which nine muscle tendons and a major nerve enter the hand from the anterior forearm. The walls and floor of the carpal tunnel are formed by the U-shaped grouping of the carpal bones, and the roof is formed by the flexor retinaculum, a strong ligament that anteriorly unites the bones.

Metacarpal Bones

The palm of the hand contains five elongated metacarpal bones. These bones lie between the carpal bones of the wrist and the bones of the fingers and thumb (see Figure 8.7). The proximal end of each metacarpal bone articulates with one of the distal carpal bones. Each of these articulations is a **carpometacarpal joint** (see Figure 8.8). The expanded distal end of each metacarpal bone articulates at the **metacarpophalangeal joint** with the proximal

forearm muscles. In addition, four major nerves for shoulder and upper limb muscles are closely associated with different regions of the humerus, and thus, humeral fractures may also damage these nerves.

Another frequent injury following a fall onto an outstretched hand is a Colles fracture ("col-lees") of the distal radius (see Figure 8.11). This involves a complete transverse fracture across the distal radius that drives the separated distal fragment of the radius posteriorly and superiorly. This injury results in a characteristic "dinner fork" bend of the forearm just above the wrist due to the posterior displacement of the hand. This is the most frequent forearm fracture and is a common injury in persons over the age of 50, particularly in older people with osteoporosis. It also commonly occurs following a high-speed fall onto the hand during activities such as snowboarding or skating.

The most commonly fractured carpal bone is the scaphoid, often resulting from a fall onto the hand. Deep pain at the lateral wrist may yield an initial diagnosis of a wrist sprain, but a radiograph taken several weeks after the injury, after tissue swelling has subsided, will reveal the fracture. Due to the poor blood supply to the scaphoid bone, healing will be slow and there is the danger of bone necrosis and subsequent degenerative joint disease of the wrist.

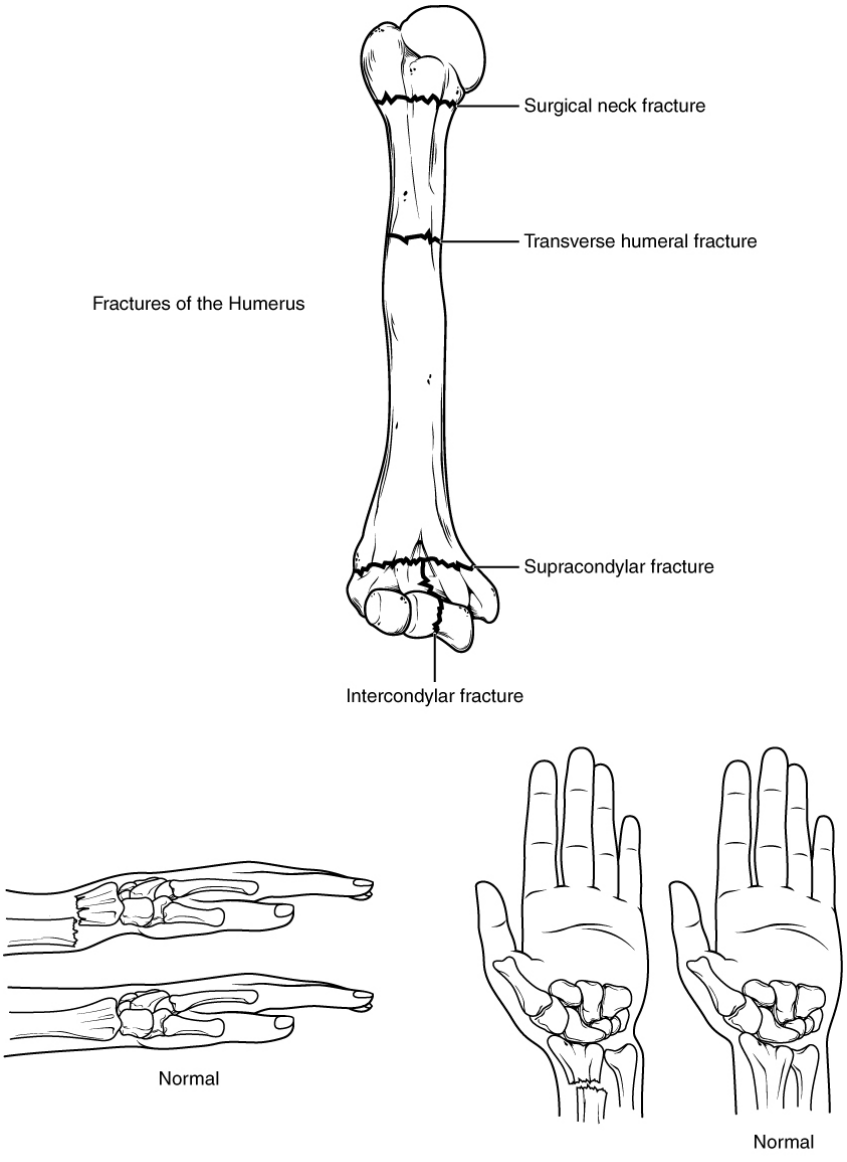


FIGURE 8.11 Fractures of the Humerus and Radius Falls or direct blows can result in fractures of the surgical neck or shaft of the humerus. Falls onto the elbow can fracture the distal humerus. A Colles fracture of the distal radius is the most common forearm fracture.

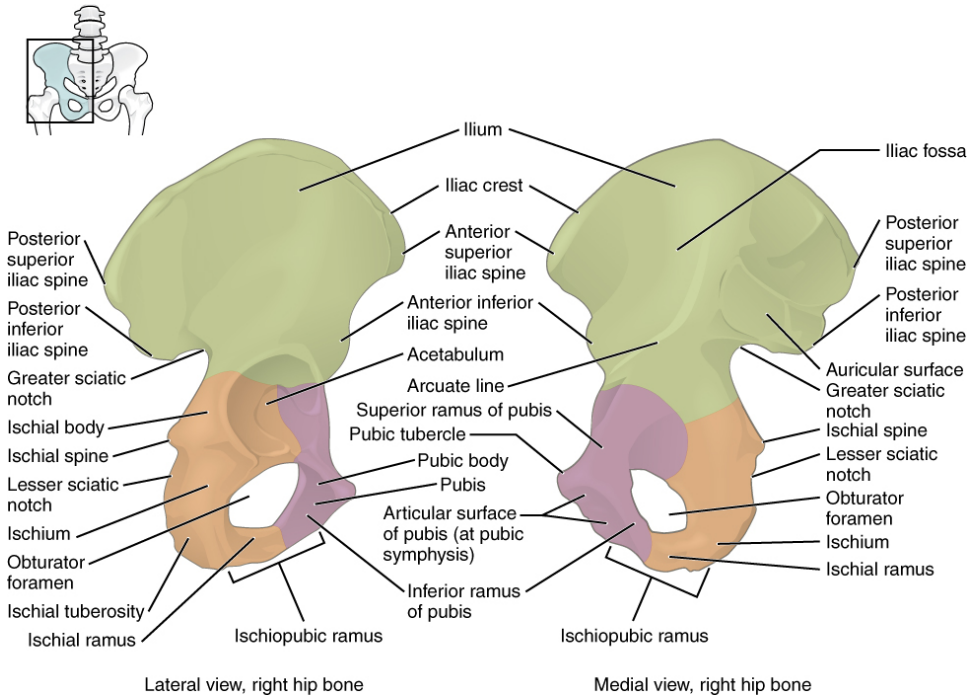


FIGURE 8.13 The Hip Bone The adult hip bone consists of three regions. The ilium forms the large, fan-shaped superior portion, the ischium forms the posteroinferior portion, and the pubis forms the anteromedial portion.

The **ilium** is the fan-like, superior region that forms the largest part of the hip bone. It is firmly united to the sacrum at the largely immobile **sacroiliac joint** (see Figure 8.12). The **ischium** forms the posteroinferior region of each hip bone. It supports the body when sitting. The **pubis** forms the anterior portion of the hip bone. The pubis curves medially, where it joins to the pubis of the opposite hip bone at a specialized joint called the **pubic symphysis**.

Ilium

When you place your hands on your waist, you can feel the arching, superior margin of the ilium along your waistline (see Figure 8.13). This curved, superior margin of the ilium is the **iliac crest**. The rounded, anterior termination of the iliac crest is the **anterior superior iliac spine**. This important bony landmark can be felt at your anterolateral hip. Inferior to the anterior superior iliac spine is a rounded protuberance called the **anterior inferior iliac spine**. Both of these iliac spines serve as attachment points for muscles of the thigh. Posteriorly, the iliac crest curves downward to terminate as the **posterior superior iliac spine**. Muscles and ligaments surround but do not cover this bony landmark, thus sometimes producing a depression seen as a “dimple” located on the lower back. More inferiorly is the **posterior inferior iliac spine**. This is located at the inferior end of a large, roughened area called the **auricular surface of the ilium**. The auricular surface articulates with the auricular surface of the sacrum to form the sacroiliac joint. Both the posterior superior and posterior inferior iliac spines serve as attachment points for the muscles and very strong ligaments that support the sacroiliac joint.

The shallow depression located on the anteromedial (internal) surface of the upper ilium is called the **iliac fossa**. The inferior margin of this space is formed by the **arcuate line of the ilium**, the ridge formed by the pronounced change in curvature between the upper and lower portions of the ilium. The large, inverted U-shaped indentation located on the posterior margin of the lower ilium is called the **greater sciatic notch**.

Ischium

The ischium forms the posterolateral portion of the hip bone (see Figure 8.13). The large, roughened area of the inferior ischium is the **ischial tuberosity**. This serves as the attachment for the posterior thigh muscles and also carries the weight of the body when sitting. You can feel the ischial tuberosity if you wiggle your pelvis against the seat of a chair. Projecting superiorly and anteriorly from the ischial tuberosity is a narrow segment of bone called the **ischial ramus**. The slightly curved posterior margin of the ischium above the ischial tuberosity is the **lesser sciatic notch**. The bony projection separating the lesser sciatic notch and greater sciatic notch is the **ischial spine**.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/3Dpelvis) for a 3-D view of the pelvis and its associated ligaments. What is the large opening in the bony pelvis, located between the ischium and pubic regions, and what two parts of the pubis contribute to the formation of this opening?

The sacrospinous and sacrotuberous ligaments also help to define two openings on the posterolateral sides of the pelvis through which muscles, nerves, and blood vessels for the lower limb exit. The superior opening is the **greater sciatic foramen**. This large opening is formed by the greater sciatic notch of the hip bone, the sacrum, and the sacrospinous ligament. The smaller, more inferior **lesser sciatic foramen** is formed by the lesser sciatic notch of the hip bone, together with the sacrospinous and sacrotuberous ligaments.

The space enclosed by the bony pelvis is divided into two regions (Figure 8.15). The broad, superior region, defined laterally by the large, fan-like portion of the upper hip bone, is called the **greater pelvis** (greater pelvic cavity; false pelvis). This broad area is occupied by portions of the small and large intestines, and because it is more closely associated with the abdominal cavity, it is sometimes referred to as the false pelvis. More inferiorly, the narrow, rounded space of the **lesser pelvis** (lesser pelvic cavity; true pelvis) contains the bladder and other pelvic organs, and thus is also known as the true pelvis. The **pelvic brim** (also known as the **pelvic inlet**) forms the superior margin of the lesser pelvis, separating it from the greater pelvis. The pelvic brim is defined by a line formed by the upper margin of the pubic symphysis anteriorly, and the pectineal line of the pubis, the arcuate line of the ilium, and the sacral promontory (the anterior margin of the superior sacrum) posteriorly. The inferior limit of the lesser pelvic cavity is called the **pelvic outlet**. This large opening is defined by the inferior margin of the pubic symphysis anteriorly, and the ischiopubic ramus, the ischial tuberosity, the sacrotuberous ligament, and the inferior tip of the coccyx posteriorly. Because of the anterior tilt of the pelvis, the lesser pelvis is also angled, giving it an anterosuperior (pelvic inlet) to posteroinferior (pelvic outlet) orientation.

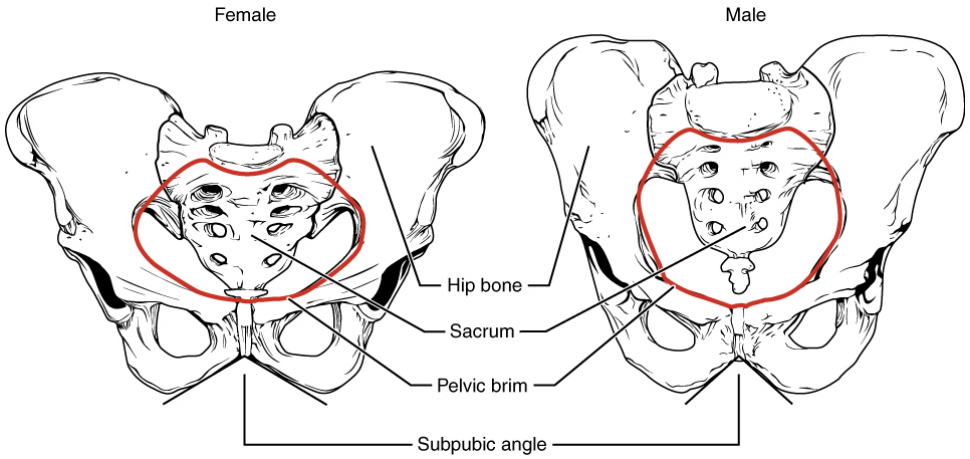


FIGURE 8.15 Male and Female Pelvis The female pelvis is adapted for childbirth and is broader, with a larger subpubic angle, a rounder pelvic brim, and a wider and more shallow lesser pelvic cavity than the male pelvis.

Comparison of the Female and Male Pelvis

The differences between the adult female and male pelvis relate to function and body size. In general, the bones of the male pelvis are thicker and heavier, adapted for support of the male's heavier physical build and stronger muscles. The greater sciatic notch of the male hip bone is narrower and deeper than the broader notch of females. Because the female pelvis is adapted for childbirth, it is wider than the male pelvis, as evidenced by the distance between the anterior superior iliac spines (see Figure 8.15). The ischial tuberosities of females are also farther apart, which increases the size of the pelvic outlet. Because of this increased pelvic width, the subpubic angle is larger in females (greater than 80 degrees) than it is in males (less than 70 degrees). The female sacrum is wider, shorter, and less curved, and the sacral promontory projects less into the pelvic cavity, thus giving the female pelvic inlet (pelvic brim) a more rounded or oval shape compared to males. The lesser pelvic cavity of females is also wider and more shallow than the narrower, deeper, and tapering lesser pelvis of males. Because of the obvious differences between female and male hip bones, this is the one bone of the body that allows for the most accurate sex determination. Table 8.1 provides an overview of the general differences between the female and male pelvis.

Like the upper limb, the lower limb is divided into three regions. The **thigh** is that portion of the lower limb located between the hip joint and knee joint. The **leg** is specifically the region between the knee joint and the ankle joint. Distal to the ankle is the **foot**. The lower limb contains 30 bones. These are the femur, patella, tibia, fibula, tarsal bones, metatarsal bones, and phalanges (see Figure 8.2). The **femur** is the single bone of the thigh. The **patella** is the kneecap and articulates with the distal femur. The **tibia** is the larger, weight-bearing bone located on the medial side of the leg, and the **fibula** is the thin bone of the lateral leg. The bones of the foot are divided into three groups. The posterior portion of the foot is formed by a group of seven bones, each of which is known as a **tarsal bone**, whereas the mid-foot contains five elongated bones, each of which is a **metatarsal bone**. The toes contain 14 small bones, each of which is a **phalanx bone of the foot**.

Femur

The femur, or thigh bone, is the single bone of the thigh region (Figure 8.16). It is the longest and strongest bone of the body, and accounts for approximately one-quarter of a person's total height. The rounded, proximal end is the **head of the femur**, which articulates with the acetabulum of the hip bone to form the **hip joint**. The **fovea capitis** is a minor indentation on the medial side of the femoral head that serves as the site of attachment for the **ligament of the head of the femur**. This ligament spans the femur and acetabulum, but is weak and provides little support for the hip joint. It does, however, carry an important artery that supplies the head of the femur.

area on the outer, lateral side of the condyle is the **lateral epicondyle of the femur**. Similarly, the smooth region of the distal and posterior medial femur is the **medial condyle of the femur**, and the irregular outer, medial side of this is the **medial epicondyle of the femur**. The lateral and medial condyles articulate with the tibia to form the knee joint. The epicondyles provide attachment for muscles and supporting ligaments of the knee. The **adductor tubercle** is a small bump located at the superior margin of the medial epicondyle. Posteriorly, the medial and lateral condyles are separated by a deep depression called the **intercondylar fossa**. Anteriorly, the smooth surfaces of the condyles join together to form a wide groove called the **patellar surface**, which provides for articulation with the patella bone. The combination of the medial and lateral condyles with the patellar surface gives the distal end of the femur a horseshoe (U) shape.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/midfemur) to view how a fracture of the mid-femur is surgically repaired. How are the two portions of the broken femur stabilized during surgical repair of a fractured femur?

Patella

The patella (kneecap) is largest sesamoid bone of the body (see Figure 8.16). A sesamoid bone is a bone that is incorporated into the tendon of a muscle where that tendon crosses a joint. The sesamoid bone articulates with the underlying bones to prevent damage to the muscle tendon due to rubbing against the bones during movements of the joint. The patella is found in the tendon of the quadriceps femoris muscle, the large muscle of the anterior thigh that passes across the anterior knee to attach to the tibia. The patella articulates with the patellar surface of the femur and thus prevents rubbing of the muscle tendon against the distal femur. The patella also lifts the tendon away from the knee joint, which increases the leverage power of the quadriceps femoris muscle as it acts across the knee. The patella does not articulate with the tibia.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/kneesurgery) to watch a virtual knee replacement surgery. The prosthetic knee components must be properly aligned to function properly. How is this alignment ensured?

HOMEOSTATIC IMBALANCES

Runner's Knee

Runner's knee, also known as patellofemoral syndrome, is the most common overuse injury among runners. It is most frequent in adolescents and young adults, and is more common in females. It often results from excessive running, particularly downhill, but may also occur in athletes who do a lot of knee bending, such as jumpers, skiers, cyclists, weight lifters, and soccer players. It is felt as a dull, aching pain around the front of the knee and deep to the patella. The pain may be felt when walking or running, going up or down stairs, kneeling or squatting, or after sitting with the knee bent for an extended period.

Patellofemoral syndrome may be initiated by a variety of causes, including individual variations in the shape and movement of the patella, a direct blow to the patella, or flat feet or improper shoes that cause excessive turning in or out of the feet or leg. These factors may cause in an imbalance in the muscle pull that acts on the patella, resulting in an abnormal tracking of the patella that allows it to deviate too far toward the lateral side of the patellar surface on the distal femur.

Because the hips are wider than the knee region, the femur has a diagonal orientation within the thigh, in contrast to the vertically oriented tibia of the leg (Figure 8.17). The Q-angle is a measure of how far the femur is angled laterally away from vertical. The Q-angle is normally 10–15 degrees, with females typically having a larger Q-angle due to their wider pelvis. During extension of the knee, the quadriceps femoris muscle pulls the patella both superiorly and laterally, with the lateral pull greater in females due to their large Q-angle. This makes females more vulnerable to developing patellofemoral syndrome than males. Normally, the large lip on the lateral side of the patellar surface of the femur compensates for the lateral pull on the patella, and thus helps to maintain its proper tracking.

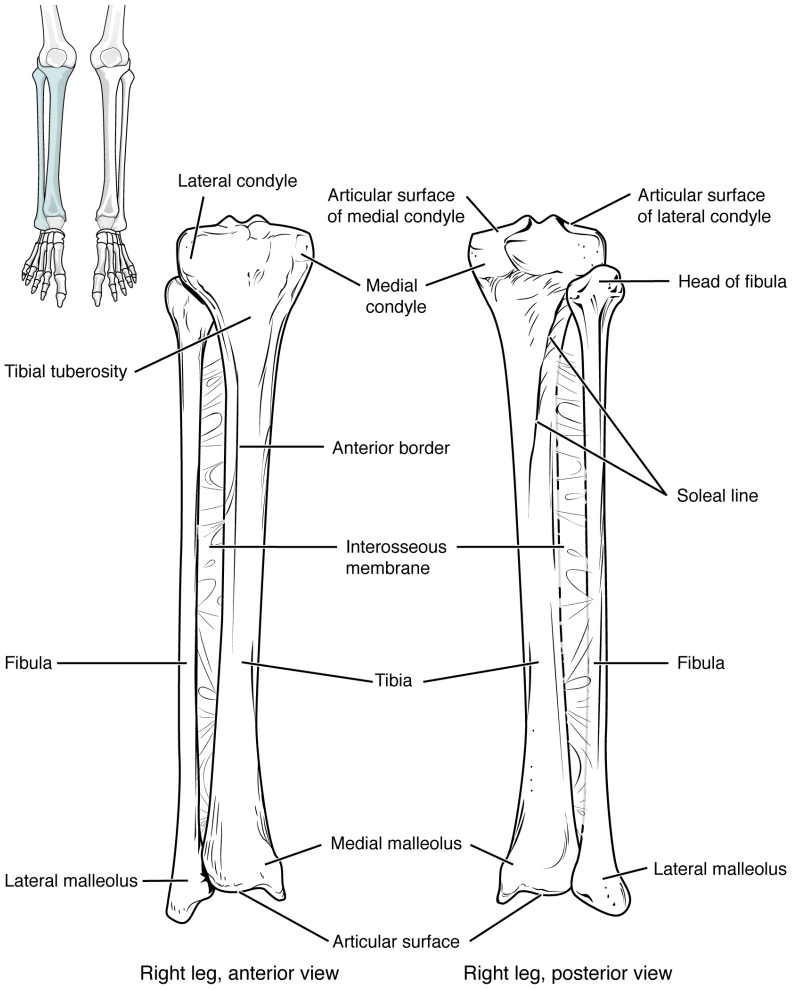


FIGURE 8.18 Tibia and Fibula The tibia is the larger, weight-bearing bone located on the medial side of the leg. The fibula is the slender bone of the lateral side of the leg and does not bear weight.

The proximal end of the tibia is greatly expanded. The two sides of this expansion form the **medial condyle of the tibia** and the **lateral condyle of the tibia**. The tibia does not have epicondyles. The top surface of each condyle is smooth and flattened. These areas articulate with the medial and lateral condyles of the femur to form the **knee joint**. Between the articulating surfaces of the tibial condyles is the **intercondylar eminence**, an irregular, elevated area that serves as the inferior attachment point for two supporting ligaments of the knee.

The **tibial tuberosity** is an elevated area on the anterior side of the tibia, near its proximal end. It is the final site of attachment for the muscle tendon associated with the patella. More inferiorly, the **shaft of the tibia** becomes triangular in shape.

The anterior apex of this triangle forms the **anterior border of the tibia**, which begins at the tibial tuberosity and runs inferiorly along the length of the tibia. Both the anterior border and the medial side of the triangular shaft are located immediately under the skin and can be easily palpated along the entire length of the tibia. A small ridge running down the lateral side of the tibial shaft is the **interosseous border of the tibia**. This is for the attachment of the **interosseous membrane of the leg**, the sheet of dense connective tissue that unites the tibia and fibula bones. Located on the posterior side of the tibia is the **soleal line**, a diagonally running, roughened ridge that begins below the base of the lateral condyle, and runs down and medially across the proximal third of the posterior tibia. Muscles of the posterior leg attach to this line.

The large expansion found on the medial side of the distal tibia is the **medial malleolus** (“little hammer”). This forms the large bony bump found on the medial side of the ankle region. Both the smooth surface on the inside of the medial malleolus and the smooth area at the distal end of the tibia articulate with the talus bone of the foot as part of the ankle joint. On the lateral side of the distal tibia is a wide groove called the **fibular notch**. This area

across its inferior surface, which provides passage for a muscle tendon. The talus bone articulates anteriorly with the **navicular** bone, which in turn articulates anteriorly with the three cuneiform ("wedge-shaped") bones. These bones are the **medial cuneiform**, the **intermediate cuneiform**, and the **lateral cuneiform**. Each of these bones has a broad superior surface and a narrow inferior surface, which together produce the transverse (medial-lateral) curvature of the foot. The navicular and lateral cuneiform bones also articulate with the medial side of the cuboid bone.

INTERACTIVE LINK

Use this tutorial (http://openstax.org/l/footbones) to review the bones of the foot. Which tarsal bones are in the proximal, intermediate, and distal groups?

Metatarsal Bones

The anterior half of the foot is formed by the five metatarsal bones, which are located between the tarsal bones of the posterior foot and the phalanges of the toes (see Figure 8.19). These elongated bones are numbered 1–5, starting with the medial side of the foot. The first metatarsal bone is shorter and thicker than the others. The second metatarsal is the longest. The **base of the metatarsal bone** is the proximal end of each metatarsal bone. These articulate with the cuboid or cuneiform bones. The base of the fifth metatarsal has a large, lateral expansion that provides for muscle attachments. This expanded base of the fifth metatarsal can be felt as a bony bump at the midpoint along the lateral border of the foot. The expanded distal end of each metatarsal is the **head of the metatarsal bone**. Each metatarsal bone articulates with the proximal phalanx of a toe to form a **metatarsophalangeal joint**. The heads of the metatarsal bones also rest on the ground and form the ball (anterior end) of the foot.

Phalanges

The toes contain a total of 14 phalanx bones (phalanges), arranged in a similar manner as the phalanges of the fingers (see Figure 8.19). The toes are numbered 1–5, starting with the big toe (**hallux**). The big toe has two phalanx bones, the proximal and distal phalanges. The remaining toes all have proximal, middle, and distal phalanges. A joint between adjacent phalanx bones is called an interphalangeal joint.

INTERACTIVE LINK

View this link (http://openstax.org/l/bunion) to learn about a bunion, a localized swelling on the medial side of the foot, next to the first metatarsophalangeal joint, at the base of the big toe. What is a bunion and what type of shoe is most likely to cause this to develop?

Arches of the Foot

When the foot comes into contact with the ground during walking, running, or jumping activities, the impact of the body weight puts a tremendous amount of pressure and force on the foot. During running, the force applied to each foot as it contacts the ground can be up to 2.5 times your body weight. The bones, joints, ligaments, and muscles of the foot absorb this force, thus greatly reducing the amount of shock that is passed superiorly into the lower limb and body. The arches of the foot play an important role in this shock-absorbing ability. When weight is applied to the foot, these arches will flatten somewhat, thus absorbing energy. When the weight is removed, the arch rebounds, giving "spring" to the step. The arches also serve to distribute body weight side to side and to either end of the foot.

The foot has a transverse arch, a medial longitudinal arch, and a lateral longitudinal arch (see Figure 8.19). The transverse arch forms the medial-lateral curvature of the mid-foot. It is formed by the wedge shapes of the cuneiform bones and bases (proximal ends) of the first to fourth metatarsal bones. This arch helps to distribute body weight from side to side within the foot, thus allowing the foot to accommodate uneven terrain.

The longitudinal arches run down the length of the foot. The lateral longitudinal arch is relatively flat, whereas the medial longitudinal arch is larger (taller). The longitudinal arches are formed by the tarsal bones posteriorly and the metatarsal bones anteriorly. These arches are supported at either end, where they contact the ground. Posteriorly, this support is provided by the calcaneus bone and anteriorly by the heads (distal ends) of the metatarsal bones. The talus bone, which receives the weight of the body, is located at the top of the longitudinal arches. Body weight is

underlying mesenchyme to rapidly proliferate, producing the outgrowth of the developing limb. As the limb bud elongates, cells located farther from the apical ectodermal ridge slow their rates of cell division and begin to differentiate. In this way, the limb develops along a proximal-to-distal axis.

During the sixth week of development, the distal ends of the upper and lower limb buds expand and flatten into a paddle shape. This region will become the hand or foot. The wrist or ankle areas then appear as a constriction that develops at the base of the paddle. Shortly after this, a second constriction on the limb bud appears at the future site of the elbow or knee. Within the paddle, areas of tissue undergo cell death, producing separations between the growing fingers and toes. Also during the sixth week of development, mesenchyme within the limb buds begins to differentiate into hyaline cartilage that will form models of the future limb bones.

The early outgrowth of the upper and lower limb buds initially has the limbs positioned so that the regions that will become the palm of the hand or the bottom of the foot are facing medially toward the body, with the future thumb or big toe both oriented toward the head. During the seventh week of development, the upper limb rotates laterally by 90 degrees, so that the palm of the hand faces anteriorly and the thumb points laterally. In contrast, the lower limb undergoes a 90-degree medial rotation, thus bringing the big toe to the medial side of the foot.

INTERACTIVE LINK

Watch this animation (http://openstax.org/l/limbbuds) to follow the development and growth of the upper and lower limb buds. On what days of embryonic development do these events occur: (a) first appearance of the upper limb bud (limb ridge); (b) the flattening of the distal limb to form the handplate or footplate; and (c) the beginning of limb rotation?

Ossification of Appendicular Bones

All of the girdle and limb bones, except for the clavicle, develop by the process of endochondral ossification. This process begins as the mesenchyme within the limb bud differentiates into hyaline cartilage to form cartilage models for future bones. By the twelfth week, a primary ossification center will have appeared in the diaphysis (shaft) region of the long bones, initiating the process that converts the cartilage model into bone. A secondary ossification center will appear in each epiphysis (expanded end) of these bones at a later time, usually after birth. The primary and secondary ossification centers are separated by the epiphyseal plate, a layer of growing hyaline cartilage. This plate is located between the diaphysis and each epiphysis. It continues to grow and is responsible for the lengthening of the bone. The epiphyseal plate is retained for many years, until the bone reaches its final, adult size, at which time the epiphyseal plate disappears and the epiphysis fuses to the diaphysis. (Seek additional content on ossification in the chapter on bone tissue.)

Small bones, such as the phalanges, will develop only one secondary ossification center and will thus have only a single epiphyseal plate. Large bones, such as the femur, will develop several secondary ossification centers, with an epiphyseal plate associated with each secondary center. Thus, ossification of the femur begins at the end of the seventh week with the appearance of the primary ossification center in the diaphysis, which rapidly expands to ossify the shaft of the bone prior to birth. Secondary ossification centers develop at later times. Ossification of the distal end of the femur, to form the condyles and epicondyles, begins shortly before birth. Secondary ossification centers also appear in the femoral head late in the first year after birth, in the greater trochanter during the fourth year, and in the lesser trochanter between the ages of 9 and 10 years. Once these areas have ossified, their fusion to the diaphysis and the disappearance of each epiphyseal plate follow a reversed sequence. Thus, the lesser trochanter is the first to fuse, doing so at the onset of puberty (around 11 years of age), followed by the greater trochanter approximately 1 year later. The femoral head fuses between the ages of 14–17 years, whereas the distal condyles of the femur are the last to fuse, between the ages of 16–19 years. Knowledge of the age at which different epiphyseal plates disappear is important when interpreting radiographs taken of children. Since the cartilage of an epiphyseal plate is less dense than bone, the plate will appear dark in a radiograph image. Thus, a normal epiphyseal plate may be mistaken for a bone fracture.

The clavicle is the one appendicular skeleton bone that does not develop via endochondral ossification. Instead, the clavicle develops through the process of intramembranous ossification. During this process, mesenchymal cells differentiate directly into bone-producing cells, which produce the clavicle directly, without first making a cartilage

Despite these difficulties, treatment for clubfoot is usually successful, and the child will grow up to lead a normal, active life. Numerous examples of individuals born with a clubfoot who went on to successful careers include Dudley Moore (comedian and actor), Damon Wayans (comedian and actor), Troy Aikman (three-time Super Bowl-winning quarterback), Kristi Yamaguchi (Olympic gold medalist in figure skating), Mia Hamm (two-time Olympic gold medalist in soccer), and Charles Woodson (Heisman trophy and Super Bowl winner).

of the ulna and the ulnar notch of the radius

distal tibiofibular joint articulation between the distal fibula and the fibular notch of the tibia

elbow joint joint located between the upper arm and forearm regions of the upper limb; formed by the articulations between the trochlea of the humerus and the trochlear notch of the ulna, and the capitulum of the humerus and the head of the radius

femur thigh bone; the single bone of the thigh

fibula thin, non-weight-bearing bone found on the lateral side of the leg

fibular notch wide groove on the lateral side of the distal tibia for articulation with the fibula at the distal tibiofibular joint

flexor retinaculum strong band of connective tissue at the anterior wrist that spans the top of the U-shaped grouping of the carpal bones to form the roof of the carpal tunnel

foot portion of the lower limb located distal to the ankle joint

forearm region of the upper limb located between the elbow and wrist joints; contains the radius and ulna bones

fossa (plural = fossae) shallow depression on the surface of a bone

fovea capitis minor indentation on the head of the femur that serves as the site of attachment for the ligament to the head of the femur

glenohumeral joint shoulder joint; formed by the articulation between the glenoid cavity of the scapula and the head of the humerus

glenoid cavity (also, glenoid fossa) shallow depression located on the lateral scapula, between the superior and lateral borders

gluteal tuberosity roughened area on the posterior side of the proximal femur, extending inferiorly from the base of the greater trochanter

greater pelvis (also, greater pelvic cavity or false pelvis) broad space above the pelvic brim defined laterally by the fan-like portion of the upper ilium

greater sciatic foramen pelvic opening formed by the greater sciatic notch of the hip bone, the sacrum, and the sacrospinous ligament

greater sciatic notch large, U-shaped indentation located on the posterior margin of the ilium, superior to the ischial spine

greater trochanter large, bony expansion of the femur that projects superiorly from the base of the femoral neck

greater tubercle enlarged prominence located on the lateral side of the proximal humerus

hallux big toe; digit 1 of the foot

hamate from the lateral side, the fourth of the four distal carpal bones; articulates with the lunate and triquetrum proximally, the fourth and fifth metacarpals distally, and the capitate laterally

hand region of the upper limb distal to the wrist joint

head of the femur rounded, proximal end of the femur that articulates with the acetabulum of the hip bone to form the hip joint

head of the fibula small, knob-like, proximal end of the fibula; articulates with the inferior aspect of the lateral condyle of the tibia

head of the humerus smooth, rounded region on the medial side of the proximal humerus; articulates with the glenoid fossa of the scapula to form the glenohumeral (shoulder) joint

head of the metatarsal bone expanded, distal end of each metatarsal bone

head of the radius disc-shaped structure that forms the proximal end of the radius; articulates with the capitulum of the humerus as part of the elbow joint, and with the radial notch of the ulna as part of the proximal radioulnar joint

head of the ulna small, rounded distal end of the ulna; articulates with the ulnar notch of the distal radius, forming the distal radioulnar joint

hip bone coxal bone; single bone that forms the pelvic girdle; consists of three areas, the ilium, ischium, and pubis

hip joint joint located at the proximal end of the lower limb; formed by the articulation between the acetabulum of the hip bone and the head of the femur

hook of the hamate bone bony extension located on the anterior side of the hamate carpal bone

humerus single bone of the upper arm

iliac crest curved, superior margin of the ilium

iliac fossa shallow depression found on the anterior and medial surfaces of the upper ilium

ilium superior portion of the hip bone

inferior angle of the scapula inferior corner of the scapula located where the medial and lateral borders meet

inferior pubic ramus narrow segment of bone that passes inferiorly and laterally from the pubic body; joins with the ischial ramus to form the ischiopubic ramus

infraglenoid tubercle small bump or roughened area located on the lateral border of the scapula, near the inferior margin of the glenoid cavity

infraspinous fossa broad depression located on the posterior scapula, inferior to the spine

intercondylar eminence irregular elevation on the superior end of the tibia, between the articulating surfaces of the medial and lateral condyles

capitis of the femoral head

limb bud small elevation that appears on the lateral side of the embryo during the fourth or fifth week of development, which gives rise to an upper or lower limb

linea aspera longitudinally running bony ridge located in the middle third of the posterior femur

lunate from the lateral side, the second of the four proximal carpal bones; articulates with the radius proximally, the capitate and hamate distally, the scaphoid laterally, and the triquetrum medially

medial border of the scapula elongated, medial margin of the scapula

medial condyle of the femur smooth, articulating surface that forms the distal and posterior sides of the medial expansion of the distal femur

medial condyle of the tibia medial, expanded region of the proximal tibia that includes the smooth surface that articulates with the medial condyle of the femur as part of the knee joint

medial cuneiform most medial of the three cuneiform tarsal bones; articulates posteriorly with the navicular bone, laterally with the intermediate cuneiform bone, and anteriorly with the first and second metatarsal bones

medial epicondyle of the femur roughened area of the distal femur located on the medial side of the medial condyle

medial epicondyle of the humerus enlarged projection located on the medial side of the distal humerus

medial malleolus bony expansion located on the medial side of the distal tibia

metacarpal bone one of the five long bones that form the palm of the hand; numbered 1–5, starting on the lateral (thumb) side of the hand

metacarpophalangeal joint articulation between the distal end of a metacarpal bone of the hand and a proximal phalanx bone of the thumb or a finger

metatarsal bone one of the five elongated bones that forms the anterior half of the foot; numbered 1–5, starting on the medial side of the foot

metatarsophalangeal joint articulation between a metatarsal bone of the foot and the proximal phalanx bone of a toe

midcarpal joint articulation between the proximal and distal rows of the carpal bones; contributes to movements of the hand at the wrist

navicular tarsal bone that articulates posteriorly with the talus bone, laterally with the cuboid bone, and anteriorly with the medial, intermediate, and lateral cuneiform bones

neck of the femur narrowed region located inferior to the head of the femur

neck of the radius narrowed region immediately distal to the head of the radius

obturator foramen large opening located in the anterior hip bone, between the pubis and ischium regions

olecranon fossa large depression located on the posterior side of the distal humerus; this space receives the olecranon process of the ulna when the elbow is fully extended

olecranon process expanded posterior and superior portions of the proximal ulna; forms the bony tip of the elbow

patella kneecap; the largest sesamoid bone of the body; articulates with the distal femur

patellar surface smooth groove located on the anterior side of the distal femur, between the medial and lateral condyles; site of articulation for the patella

pectineal line narrow ridge located on the superior surface of the superior pubic ramus

pectoral girdle shoulder girdle; the set of bones, consisting of the scapula and clavicle, which attaches each upper limb to the axial skeleton

pelvic brim pelvic inlet; the dividing line between the greater and lesser pelvic regions; formed by the superior margin of the pubic symphysis, the pectineal lines of each pubis, the arcuate lines of each ilium, and the sacral promontory

pelvic girdle hip girdle; consists of a single hip bone, which attaches a lower limb to the sacrum of the axial skeleton

pelvic inlet pelvic brim

pelvic outlet inferior opening of the lesser pelvis; formed by the inferior margin of the pubic symphysis, right and left ischiopubic rami and sacrotuberous ligaments, and the tip of the coccyx

pelvis ring of bone consisting of the right and left hip bones, the sacrum, and the coccyx

phalanx bone of the foot (plural = phalanges) one of the 14 bones that form the toes; these include the proximal and distal phalanges of the big toe, and the proximal, middle, and distal phalanx bones of toes two through five

phalanx bone of the hand (plural = phalanges) one of the 14 bones that form the thumb and fingers; these include the proximal and distal phalanges of the thumb, and the proximal, middle, and distal phalanx bones of the fingers two through five

pisiform from the lateral side, the fourth of the four proximal carpal bones; articulates with the anterior surface of the triquetrum

pollex (also, thumb) digit 1 of the hand

sustentaculum tali bony ledge extending from the medial side of the calcaneus bone

talus tarsal bone that articulates superiorly with the tibia and fibula at the ankle joint; also articulates inferiorly with the calcaneus bone and anteriorly with the navicular bone

tarsal bone one of the seven bones that make up the posterior foot; includes the calcaneus, talus, navicular, cuboid, medial cuneiform, intermediate cuneiform, and lateral cuneiform bones

thigh portion of the lower limb located between the hip and knee joints

tibia shin bone; the large, weight-bearing bone located on the medial side of the leg

tibial tuberosity elevated area on the anterior surface of the proximal tibia

trapezium from the lateral side, the first of the four distal carpal bones; articulates with the scaphoid proximally, the first and second metacarpals distally, and the trapezoid medially

trapezoid from the lateral side, the second of the four distal carpal bones; articulates with the scaphoid proximally, the second metacarpal distally, the trapezium laterally, and the capitate medially

triquetrum from the lateral side, the third of the four proximal carpal bones; articulates with the lunate laterally, the hamate distally, and has a facet for the pisiform

trochlea pulley-shaped region located medially at the distal end of the humerus; articulates at the elbow with the trochlear notch of the ulna

trochlear notch large, C-shaped depression located on the anterior side of the proximal ulna; articulates at the elbow with the trochlea of the humerus

ulna bone located on the medial side of the forearm

ulnar notch of the radius shallow, smooth area located on the medial side of the distal radius; articulates with the head of the ulna at the distal radioulnar joint

ulnar tuberosity roughened area located on the anterior, proximal ulna inferior to the coronoid process

Chapter Review

8.1 The Pectoral Girdle

The pectoral girdle, consisting of the clavicle and the scapula, attaches each upper limb to the axial skeleton. The clavicle is an anterior bone whose sternal end articulates with the manubrium of the sternum at the sternoclavicular joint. The sternal end is also anchored to the first rib by the costoclavicular ligament. The acromial end of the clavicle articulates with the acromion of the scapula at the acromioclavicular joint. This end is also anchored to the coracoid process of the scapula by the coracoclavicular ligament, which provides indirect support for the acromioclavicular joint. The clavicle supports the scapula, transmits the weight and forces from the upper limb to the body trunk, and protects the underlying nerves and blood vessels.

The scapula lies on the posterior aspect of the pectoral girdle. It mediates the attachment of the upper limb to the clavicle, and contributes to the formation of the glenohumeral (shoulder) joint. This triangular bone has three sides called the medial, lateral, and superior borders. The suprascapular notch is located on the superior border. The scapula also has three corners, two of which are the superior and inferior angles. The third corner is occupied by the glenoid cavity. Posteriorly, the spine separates the supraspinous and infraspinous fossae, and then extends laterally as the acromion. The subscapular fossa is located on the anterior surface of the scapula. The coracoid process projects anteriorly, passing inferior to the lateral end of the clavicle.

8.2 Bones of the Upper Limb

Each upper limb is divided into three regions and contains a total of 30 bones. The upper arm is the region located between the shoulder and elbow joints. This area contains the humerus. The proximal humerus consists of the head, which articulates with the scapula at the glenohumeral joint, the greater and lesser tubercles separated by the intertubercular (bicipital) groove, and the anatomical and surgical necks. The humeral shaft has the roughened area of the deltoid tuberosity on its lateral side. The distal humerus is flattened, forming a lateral supracondylar ridge that terminates at the small lateral epicondyle. The medial side of the distal humerus has the large, medial epicondyle. The articulating surfaces of the distal humerus consist of the trochlea medially and the capitulum laterally. Depressions on the humerus that accommodate the forearm bones during bending (flexing) and straightening (extending) of the elbow include the coronoid fossa, the radial fossa, and the olecranon fossa.

The forearm is the region of the upper limb located between the elbow and wrist joints. This region contains two bones, the ulna medially and the radius on the lateral (thumb) side. The elbow joint is formed by the articulation between the trochlea of the humerus and the trochlear notch of the ulna, plus the

8.4 Bones of the Lower Limb

The lower limb is divided into three regions. These are the thigh, located between the hip and knee joints; the leg, located between the knee and ankle joints; and distal to the ankle, the foot. There are 30 bones in each lower limb. These are the femur, patella, tibia, fibula, seven tarsal bones, five metatarsal bones, and 14 phalanges.

The femur is the single bone of the thigh. Its rounded head articulates with the acetabulum of the hip bone to form the hip joint. The head has the fovea capitis for attachment of the ligament of the head of the femur. The narrow neck joins inferiorly with the greater and lesser trochanters. Passing between these bony expansions are the intertrochanteric line on the anterior femur and the larger intertrochanteric crest on the posterior femur. On the posterior shaft of the femur is the gluteal tuberosity proximally and the linea aspera in the mid-shaft region. The expanded distal end consists of three articulating surfaces: the medial and lateral condyles, and the patellar surface. The outside margins of the condyles are the medial and lateral epicondyles. The adductor tubercle is on the superior aspect of the medial epicondyle.

The patella is a sesamoid bone located within a muscle tendon. It articulates with the patellar surface on the anterior side of the distal femur, thereby protecting the muscle tendon from rubbing against the femur.

The leg contains the large tibia on the medial side and the slender fibula on the lateral side. The tibia bears the weight of the body, whereas the fibula does not bear weight. The interosseous border of each bone is the attachment site for the interosseous membrane of the leg, the connective tissue sheet that unites the tibia and fibula.

The proximal tibia consists of the expanded medial and lateral condyles, which articulate with the medial and lateral condyles of the femur to form the knee joint. Between the tibial condyles is the intercondylar eminence. On the anterior side of the proximal tibia is the tibial tuberosity, which is continuous inferiorly with the anterior border of the tibia. On the posterior side, the proximal tibia has the curved soleal line. The bony expansion on the medial side of the distal tibia is the medial malleolus. The groove on the lateral side of the distal tibia is the fibular notch.

The head of the fibula forms the proximal end and articulates with the underside of the lateral condyle of the tibia. The distal fibula articulates with the fibular notch of the tibia. The expanded distal end of the fibula is the lateral malleolus.

The posterior foot is formed by the seven tarsal bones. The talus articulates superiorly with the distal tibia, the medial malleolus of the tibia, and the lateral malleolus of the fibula to form the ankle joint. The talus articulates inferiorly with the calcaneus bone. The sustentaculum tali of the calcaneus helps to support the talus. Anterior to the talus is the navicular bone, and anterior to this are the medial, intermediate, and lateral cuneiform bones. The cuboid bone is anterior to the calcaneus.

The five metatarsal bones form the anterior foot. The base of these bones articulate with the cuboid or cuneiform bones. The metatarsal heads, at their distal ends, articulate with the proximal phalanges of the toes. The big toe (toe number 1) has proximal and distal phalanx bones. The remaining toes have proximal, middle, and distal phalanges.

8.5 Development of the Appendicular Skeleton

The bones of the appendicular skeleton arise from embryonic mesenchyme. Limb buds appear at the end of the fourth week. The apical ectodermal ridge, located at the end of the limb bud, stimulates growth and elongation of the limb. During the sixth week, the distal end of the limb bud becomes paddle-shaped, and selective cell death separates the developing fingers and toes. At the same time, mesenchyme within the limb bud begins to differentiate into hyaline cartilage, forming models for future bones. During the seventh week, the upper limbs rotate laterally and the lower limbs rotate medially, bringing the limbs into their final positions.

Endochondral ossification, the process that converts the hyaline cartilage model into bone, begins in most appendicular bones by the twelfth fetal week. This begins as a primary ossification center in the diaphysis, followed by the later appearance of one or more secondary ossifications centers in the regions of the epiphyses. Each secondary ossification center is separated from the primary ossification center by an epiphyseal plate. Continued growth of the epiphyseal plate cartilage provides for bone lengthening. Disappearance of the epiphyseal plate is followed by fusion of the bony components to form a single, adult bone.

The clavicle develops via intramembranous ossification, in which mesenchyme is converted directly into bone tissue. Ossification within the clavicle begins during the fifth week of development and

16. Which bony landmark is located on the lateral side of the proximal humerus?
a. greater tubercle
b. trochlea
c. lateral epicondyle
d. lesser tubercle

17. Which region of the humerus articulates with the radius as part of the elbow joint?
a. trochlea
b. styloid process
c. capitulum
d. olecranon process

18. Which is the lateral-most carpal bone of the proximal row?
a. trapezium
b. hamate
c. pisiform
d. scaphoid

19. The radius bone _____.
a. is found on the medial side of the forearm
b. has a head that articulates with the radial notch of the ulna
c. does not articulate with any of the carpal bones
d. has the radial tuberosity located near its distal end

20. How many bones fuse in adulthood to form the hip bone?
a. 2
b. 3
c. 4
d. 5

21. Which component forms the superior part of the hip bone?
a. ilium
b. pubis
c. ischium
d. sacrum

22. Which of the following supports body weight when sitting?
a. iliac crest
b. ischial tuberosity
c. ischiopubic ramus
d. pubic body

23. The ischial spine is found between which of the following structures?
a. inferior pubic ramus and ischial ramus
b. pectineal line and arcuate line
c. lesser sciatic notch and greater sciatic notch
d. anterior superior iliac spine and posterior superior iliac spine

24. The pelvis _____.
a. has a subpubic angle that is larger in females
b. consists of the two hip bones, but does not include the sacrum or coccyx
c. has an obturator foramen, an opening that is defined in part by the sacrospinous and sacrotuberous ligaments
d. has a space located inferior to the pelvic brim called the greater pelvis

25. Which bony landmark of the femur serves as a site for muscle attachments?
a. fovea capitis
b. lesser trochanter
c. head
d. medial condyle

26. What structure contributes to the knee joint?
a. lateral malleolus of the fibula
b. tibial tuberosity
c. medial condyle of the tibia
d. lateral epicondyle of the femur

27. Which tarsal bone articulates with the tibia and fibula?
a. calcaneus
b. cuboid
c. navicular
d. talus

28. What is the total number of bones found in the foot and toes?
a. 7
b. 14
c. 26
d. 30

29. The tibia _____.
a. has an expanded distal end called the lateral malleolus
b. is not a weight-bearing bone
c. is firmly anchored to the fibula by an interosseous membrane
d. can be palpated (felt) under the skin only at its proximal and distal ends

space filled with lubricating fluid, which allows the bones to move smoothly against each other. These joints provide greater mobility, but since the bones are free to move in relation to each other, the joint is less stable. Most of the joints between the bones of the appendicular skeleton are this freely moveable type of joint. These joints allow the muscles of the body to pull on a bone and thereby produce movement of that body region. Your ability to kick a soccer ball, pick up a fork, and dance the tango depend on mobility at these types of joints.

9.1 Classification of Joints

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Distinguish between the functional and structural classifications for joints
- Describe the three functional types of joints and give an example of each
- List the three types of diarthrodial joints

A **joint**, also called an **articulation**, is any place where adjacent bones or bone and cartilage come together (articulate with each other) to form a connection. Joints are classified both structurally and functionally. Structural classifications of joints take into account whether the adjacent bones are strongly anchored to each other by fibrous connective tissue or cartilage, or whether the adjacent bones articulate with each other within a fluid-filled space called a **joint cavity**. Functional classifications describe the degree of movement available between the bones, ranging from immobile, to slightly mobile, to freely moveable joints. The amount of movement available at a particular joint of the body is related to the functional requirements for that joint. Thus immobile or slightly moveable joints serve to protect internal organs, give stability to the body, and allow for limited body movement. In contrast, freely moveable joints allow for much more extensive movements of the body and limbs.

Structural Classification of Joints

The structural classification of joints is based on whether the articulating surfaces of the adjacent bones are directly connected by fibrous connective tissue or cartilage, or whether the articulating surfaces contact each other within a fluid-filled joint cavity. These differences serve to divide the joints of the body into three structural classifications. A **fibrous joint** is where the adjacent bones are united by fibrous connective tissue. At a **cartilaginous joint**, the bones are joined by hyaline cartilage or fibrocartilage. At a **synovial joint**, the articulating surfaces of the bones are not directly connected, but instead come into contact with each other within a joint cavity that is filled with a lubricating fluid. Synovial joints allow for free movement between the bones and are the most common joints of the body.

Functional Classification of Joints

The functional classification of joints is determined by the amount of mobility found between the adjacent bones. Joints are thus functionally classified as a synarthrosis or immobile joint, an amphiarthrosis or slightly moveable joint, or as a diarthrosis, which is a freely moveable joint (arthroun = “to fasten by a joint”). Depending on their location, fibrous joints may be functionally classified as a synarthrosis (immobile joint) or an amphiarthrosis (slightly mobile joint). Cartilaginous joints are also functionally classified as either a synarthrosis or an amphiarthrosis joint. All synovial joints are functionally classified as a diarthrosis joint.

Synarthrosis

An immobile or nearly immobile joint is called a **synarthrosis**. The immobile nature of these joints provide for a strong union between the articulating bones. This is important at locations where the bones provide protection for internal organs. Examples include sutures, the fibrous joints between the bones of the skull that surround and protect the brain (Figure 9.2), and the manubriosternal joint, the cartilaginous joint that unites the manubrium and body of the sternum for protection of the heart.

biaxial (for movement in two planes), or multiaxial joints (for movement in all three anatomical planes).

A **uniaxial joint** only allows for a motion in a single plane (around a single axis). The elbow joint, which only allows for bending or straightening, is an example of a uniaxial joint. A **biaxial joint** allows for motions within two planes. An example of a biaxial joint is a metacarpophalangeal joint (knuckle joint) of the hand. The joint allows for movement along one axis to produce bending or straightening of the finger, and movement along a second axis, which allows for spreading of the fingers away from each other and bringing them together. A joint that allows for the several directions of movement is called a **multiaxial joint** (polyaxial or triaxial joint). This type of diarthrotic joint allows for movement along three axes (Figure 9.4). The shoulder and hip joints are multiaxial joints. They allow the upper or lower limb to move in an anterior-posterior direction and a medial-lateral direction. In addition, the limb can also be rotated around its long axis. This third movement results in rotation of the limb so that its anterior surface is moved either toward or away from the midline of the body.

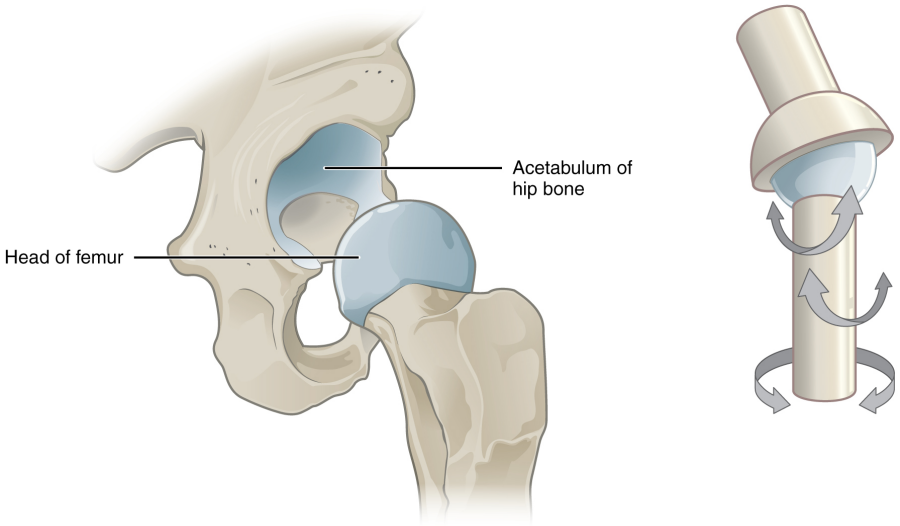


FIGURE 9.4 Multiaxial Joint A multiaxial joint, such as the hip joint, allows for three types of movement: anterior-posterior, medial-lateral, and rotational.

9.2 Fibrous Joints

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structural features of fibrous joints
- Distinguish between a suture, syndesmosis, and gomphosis
- Give an example of each type of fibrous joint

At a fibrous joint, the adjacent bones are directly connected to each other by fibrous connective tissue, and thus the bones do not have a joint cavity between them (Figure 9.5). The gap between the bones may be narrow or wide. There are three types of fibrous joints. A suture is the narrow fibrous joint found between most bones of the skull. At a syndesmosis joint, the bones are more widely separated but are held together by a narrow band of fibrous connective tissue called a **ligament** or a wide sheet of connective tissue called an interosseous membrane. This type of fibrous joint is found between the shaft regions of the long bones in the forearm and in the leg. Lastly, a gomphosis is the narrow fibrous joint between the roots of a tooth and the bony socket in the jaw into which the tooth fits.

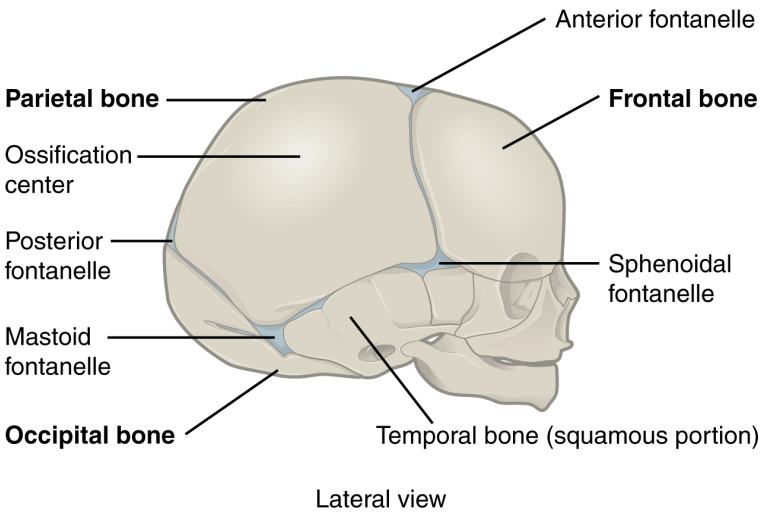


FIGURE 9.6 The Newborn Skull The fontanelles of a newborn's skull are broad areas of fibrous connective tissue that form fibrous joints between the bones of the skull.

Syndesmosis

A **syndesmosis** ("fastened with a band") is a type of fibrous joint in which two parallel bones are united to each other by fibrous connective tissue. The gap between the bones may be narrow, with the bones joined by ligaments, or the gap may be wide and filled in by a broad sheet of connective tissue called an **interosseous membrane**.

In the forearm, the wide gap between the shaft portions of the radius and ulna bones are strongly united by an interosseous membrane (see Figure 9.5**b**). Similarly, in the leg, the shafts of the tibia and fibula are also united by an interosseous membrane. In addition, at the distal tibiofibular joint, the articulating surfaces of the bones lack cartilage and the narrow gap between the bones is anchored by fibrous connective tissue and ligaments on both the anterior and posterior aspects of the joint. Together, the interosseous membrane and these ligaments form the tibiofibular syndesmosis.

The syndesmoses found in the forearm and leg serve to unite parallel bones and prevent their separation. However, a syndesmosis does not prevent all movement between the bones, and thus this type of fibrous joint is functionally classified as an amphiarthrosis. In the leg, the syndesmosis between the tibia and fibula strongly unites the bones, allows for little movement, and firmly locks the talus bone in place between the tibia and fibula at the ankle joint. This provides strength and stability to the leg and ankle, which are important during weight bearing. In the forearm, the interosseous membrane is flexible enough to allow for rotation of the radius bone during forearm movements. Thus in contrast to the stability provided by the tibiofibular syndesmosis, the flexibility of the antebrachial interosseous membrane allows for the much greater mobility of the forearm.

The interosseous membranes of the leg and forearm also provide areas for muscle attachment. Damage to a syndesmotic joint, which usually results from a fracture of the bone with an accompanying tear of the interosseous membrane, will produce pain, loss of stability of the bones, and may damage the muscles attached to the interosseous membrane. If the fracture site is not properly immobilized with a cast or splint, contractile activity by these muscles can cause improper alignment of the broken bones during healing.

Gomphosis

A **gomphosis** ("fastened with bolts") is the specialized fibrous joint that anchors the root of a tooth into its bony socket within the maxillary bone (upper jaw) or mandible bone (lower jaw) of the skull. A gomphosis is also known as a peg-and-socket joint. Spanning between the bony walls of the socket and the root of the tooth are numerous short bands of dense connective tissue, each of which is called a **periodontal ligament** (see Figure 9.5**c**). Due to the immobility of a gomphosis, this type of joint is functionally classified as a synarthrosis.

INTERACTIVE LINK

Visit this website (http://openstax.org/l/childhand) to view a radiograph (X-ray image) of a child's hand and wrist. The growing bones of child have an epiphyseal plate that forms a synchondrosis between the shaft and end of a long bone. Being less dense than bone, the area of epiphyseal cartilage is seen on this radiograph as the dark epiphyseal gaps located near the ends of the long bones, including the radius, ulna, metacarpal, and phalanx bones. Which of the bones in this image do not show an epiphyseal plate (epiphyseal gap)?

Examples of permanent synchondroses are found in the thoracic cage. One example is the first sternocostal joint, where the first rib is anchored to the manubrium by its costal cartilage. (The articulations of the remaining costal cartilages to the sternum are all synovial joints.) Additional synchondroses are formed where the anterior end of the other 11 ribs is joined to its costal cartilage. Unlike the temporary synchondroses of the epiphyseal plate, these permanent synchondroses retain their hyaline cartilage and thus do not ossify with age. Due to the lack of movement between the bone and cartilage, both temporary and permanent synchondroses are functionally classified as a synarthrosis.

Symphysis

A cartilaginous joint where the bones are joined by fibrocartilage is called a **symphysis** ("growing together"). Fibrocartilage is very strong because it contains numerous bundles of thick collagen fibers, thus giving it a much greater ability to resist pulling and bending forces when compared with hyaline cartilage. This gives symphyses the ability to strongly unite the adjacent bones, but can still allow for limited movement to occur. Thus, a symphysis is functionally classified as an amphiarthrosis.

The gap separating the bones at a symphysis may be narrow or wide. Examples in which the gap between the bones is narrow include the pubic symphysis and the manubriosternal joint. At the pubic symphysis, the pubic portions of the right and left hip bones of the pelvis are joined together by fibrocartilage across a narrow gap. Similarly, at the manubriosternal joint, fibrocartilage unites the manubrium and body portions of the sternum.

The intervertebral symphysis is a wide symphysis located between the bodies of adjacent vertebrae of the vertebral column. Here a thick pad of fibrocartilage called an intervertebral disc strongly unites the adjacent vertebrae by filling the gap between them. The width of the intervertebral symphysis is important because it allows for small movements between the adjacent vertebrae. In addition, the thick intervertebral disc provides cushioning between the vertebrae, which is important when carrying heavy objects or during high-impact activities such as running or jumping.

9.4 Synovial Joints

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structural features of a synovial joint
- Discuss the function of additional structures associated with synovial joints
- List the six types of synovial joints and give an example of each

Synovial joints are the most common type of joint in the body (Figure 9.8). A key structural characteristic for a synovial joint that is not seen at fibrous or cartilaginous joints is the presence of a joint cavity. This fluid-filled space is the site at which the articulating surfaces of the bones contact each other. Also unlike fibrous or cartilaginous joints, the articulating bone surfaces at a synovial joint are not directly connected to each other with fibrous connective tissue or cartilage. This gives the bones of a synovial joint the ability to move smoothly against each other, allowing for increased joint mobility.

the body will automatically increase the overall strength of contraction of the muscles crossing that joint, thus allowing the muscle and its tendon to serve as a "dynamic ligament" to resist forces and support the joint. This type of indirect support by muscles is very important at the shoulder joint, for example, where the ligaments are relatively weak.

Additional Structures Associated with Synovial Joints

A few synovial joints of the body have a fibrocartilage structure located between the articulating bones. This is called an **articular disc**, which is generally small and oval-shaped, or a **meniscus**, which is larger and C-shaped. These structures can serve several functions, depending on the specific joint. In some places, an articular disc may act to strongly unite the bones of the joint to each other. Examples of this include the articular discs found at the sternoclavicular joint or between the distal ends of the radius and ulna bones. At other synovial joints, the disc can provide shock absorption and cushioning between the bones, which is the function of each meniscus within the knee joint. Finally, an articular disc can serve to smooth the movements between the articulating bones, as seen at the temporomandibular joint. Some synovial joints also have a fat pad, which can serve as a cushion between the bones.

Additional structures located outside of a synovial joint serve to prevent friction between the bones of the joint and the overlying muscle tendons or skin. A **bursa** (plural = bursae) is a thin connective tissue sac filled with lubricating liquid. They are located in regions where skin, ligaments, muscles, or muscle tendons can rub against each other, usually near a body joint (Figure 9.9). Bursae reduce friction by separating the adjacent structures, preventing them from rubbing directly against each other. Bursae are classified by their location. A **subcutaneous bursa** is located between the skin and an underlying bone. It allows skin to move smoothly over the bone. Examples include the prepatellar bursa located over the kneecap and the olecranon bursa at the tip of the elbow. A **submuscular bursa** is found between a muscle and an underlying bone, or between adjacent muscles. These prevent rubbing of the muscle during movements. A large submuscular bursa, the trochanteric bursa, is found at the lateral hip, between the greater trochanter of the femur and the overlying gluteus maximus muscle. A **subtendinous bursa** is found between a tendon and a bone. Examples include the subacromial bursa that protects the tendon of shoulder muscle as it passes under the acromion of the scapula, and the suprapatellar bursa that separates the tendon of the large anterior thigh muscle from the distal femur just above the knee.

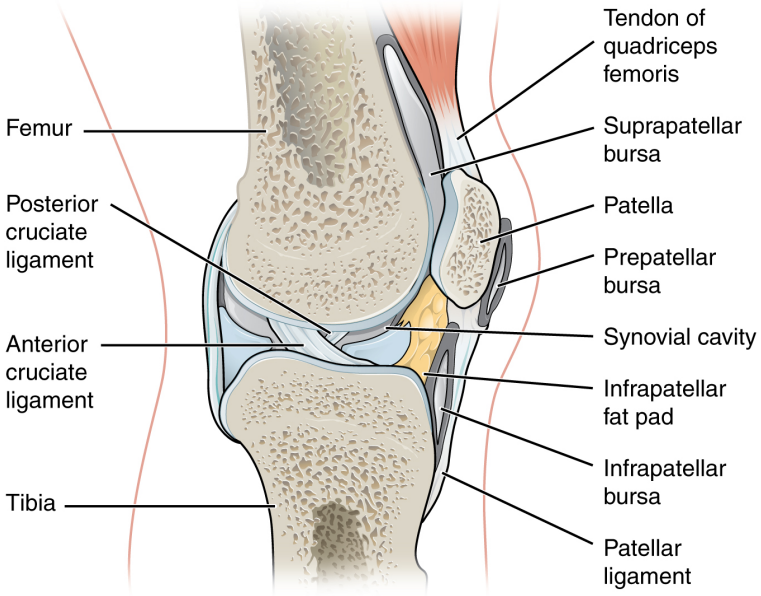


FIGURE 9.9 Bursae Bursae are fluid-filled sacs that serve to prevent friction between skin, muscle, or tendon and an underlying bone. Three major bursae and a fat pad are part of the complex joint that unites the femur and tibia of the leg.

A **tendon sheath** is similar in structure to a bursa, but smaller. It is a connective tissue sac that surrounds a muscle tendon at places where the tendon crosses a joint. It contains a lubricating fluid that allows for smooth motions of the tendon during muscle contraction and joint movements.

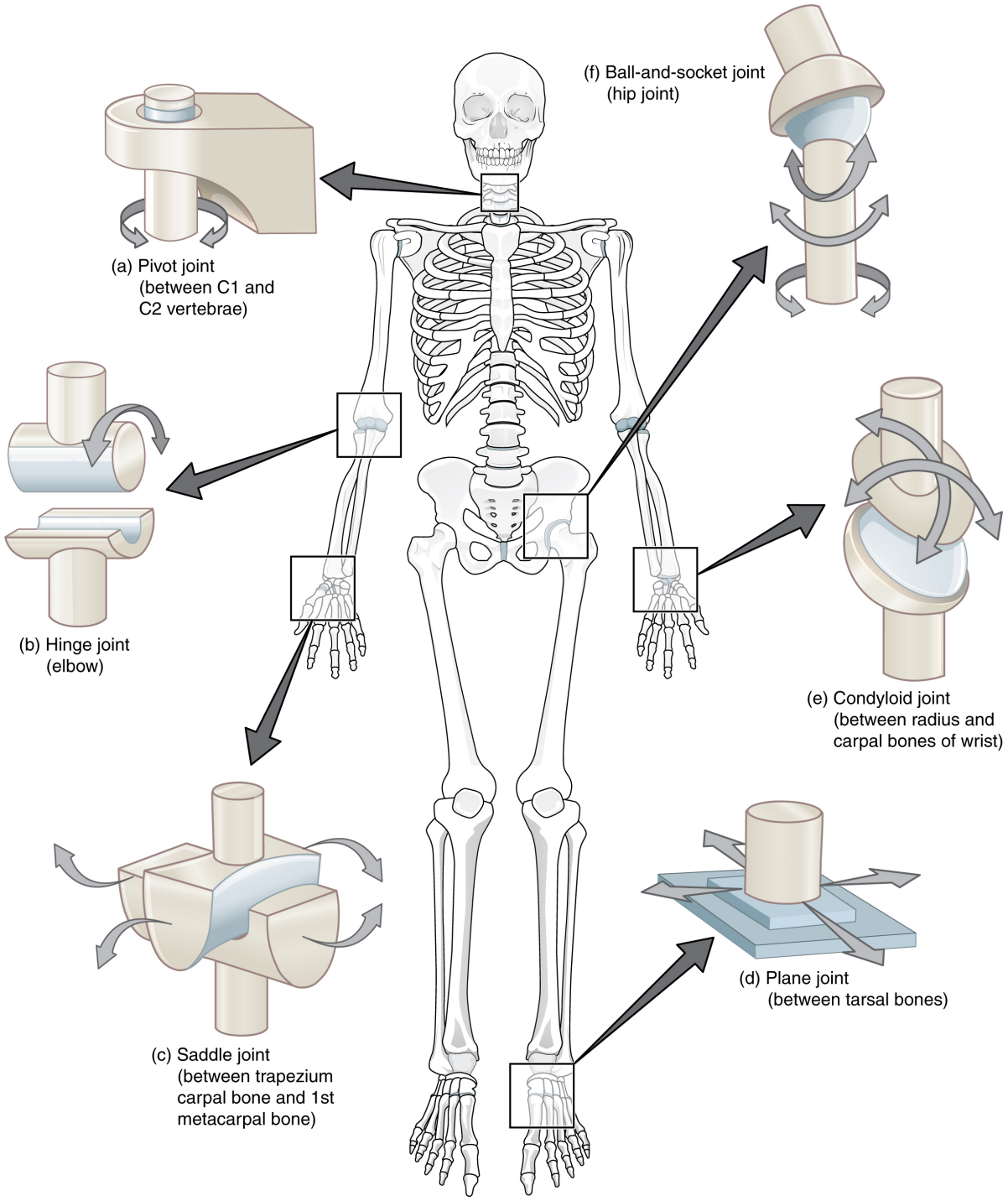


FIGURE 9.10 Types of Synovial Joints The six types of synovial joints allow the body to move in a variety of ways. (a) Pivot joints allow for rotation around an axis, such as between the first and second cervical vertebrae, which allows for side-to-side rotation of the head. (b) The hinge joint of the elbow works like a door hinge. (c) The articulation between the trapezium carpal bone and the first metacarpal bone at the base of the thumb is a saddle joint. (d) Plane joints, such as those between the tarsal bones of the foot, allow for limited gliding movements between bones. (e) The radiocarpal joint of the wrist is a condyloid joint. (f) The hip and shoulder joints are the only ball-and-socket joints of the body.

Pivot Joint

At a **pivot joint**, a rounded portion of a bone is enclosed within a ring formed partially by the articulation with another bone and partially by a ligament (see Figure 9.10**a**). The bone rotates within this ring. Since the rotation is around a single axis, pivot joints are functionally classified as a uniaxial diarthrosis type of joint. An example of a pivot joint is the atlantoaxial joint, found between the C1 (atlas) and C2 (axis) vertebrae. Here, the upward projecting dens of the axis articulates with the inner aspect of the atlas, where it is held in place by a ligament. Rotation at this

INTERACTIVE LINK

Watch this video (http://openstax.org/l/synjoints) to see an animation of synovial joints in action. Synovial joints are places where bones articulate with each other inside of a joint cavity. The different types of synovial joints are the ball-and-socket joint (shoulder joint), hinge joint (knee), pivot joint (atlantoaxial joint, between C1 and C2 vertebrae of the neck), condyloid joint (radiocarpal joint of the wrist), saddle joint (first carpometacarpal joint, between the trapezium carpal bone and the first metacarpal bone, at the base of the thumb), and plane joint (facet joints of vertebral column, between superior and inferior articular processes). Which type of synovial joint allows for the widest range of motion?

Aging and the...

Joints

Arthritis is a common disorder of synovial joints that involves inflammation of the joint. This often results in significant joint pain, along with swelling, stiffness, and reduced joint mobility. There are more than 100 different forms of arthritis. Arthritis may arise from aging, damage to the articular cartilage, autoimmune diseases, bacterial or viral infections, or unknown (probably genetic) causes.

The most common type of arthritis is osteoarthritis, which is associated with aging and "wear and tear" of the articular cartilage (Figure 9.11). Risk factors that may lead to osteoarthritis later in life include injury to a joint; jobs that involve physical labor; sports with running, twisting, or throwing actions; and being overweight. These factors put stress on the articular cartilage that covers the surfaces of bones at synovial joints, causing the cartilage to gradually become thinner. As the articular cartilage layer wears down, more pressure is placed on the bones. The joint responds by increasing production of the lubricating synovial fluid, but this can lead to swelling of the joint cavity, causing pain and joint stiffness as the articular capsule is stretched. The bone tissue underlying the damaged articular cartilage also responds by thickening, producing irregularities and causing the articulating surface of the bone to become rough or bumpy. Joint movement then results in pain and inflammation. In its early stages, symptoms of osteoarthritis may be reduced by mild activity that "warms up" the joint, but the symptoms may worsen following exercise. In individuals with more advanced osteoarthritis, the affected joints can become more painful and therefore are difficult to use effectively, resulting in increased immobility. There is no cure for osteoarthritis, but several treatments can help alleviate the pain. Treatments may include lifestyle changes, such as weight loss and low-impact exercise, and over-the-counter or prescription medications that help to alleviate the pain and inflammation. For severe cases, joint replacement surgery (arthroplasty) may be required.

Joint replacement is a very invasive procedure, so other treatments are always tried before surgery. However arthroplasty can provide relief from chronic pain and can enhance mobility within a few months following the surgery. This type of surgery involves replacing the articular surfaces of the bones with prosthesis (artificial components). For example, in hip arthroplasty, the worn or damaged parts of the hip joint, including the head and neck of the femur and the acetabulum of the pelvis, are removed and replaced with artificial joint components. The replacement head for the femur consists of a rounded ball attached to the end of a shaft that is inserted inside the diaphysis of the femur. The acetabulum of the pelvis is reshaped and a replacement socket is fitted into its place. The parts, which are always built in advance of the surgery, are sometimes custom made to produce the best possible fit for a patient.

Gout is a form of arthritis that results from the deposition of uric acid crystals within a body joint. Usually only one or a few joints are affected, such as the big toe, knee, or ankle. The attack may only last a few days, but may return to the same or another joint. Gout occurs when the body makes too much uric acid or the kidneys do not properly excrete it. A diet with excessive fructose has been implicated in raising the chances of a susceptible individual developing gout.

Other forms of arthritis are associated with various autoimmune diseases, bacterial infections of the joint, or unknown genetic causes. Autoimmune diseases, including rheumatoid arthritis, scleroderma, or systemic lupus erythematosus, produce arthritis because the immune system of the body attacks the body joints. In

described in relation to the anatomical position of the body: upright stance, with upper limbs to the side of body and palms facing forward. Refer to Figure 9.12 as you go through this section.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/anatomical) to learn about anatomical motions. What motions involve increasing or decreasing the angle of the foot at the ankle?

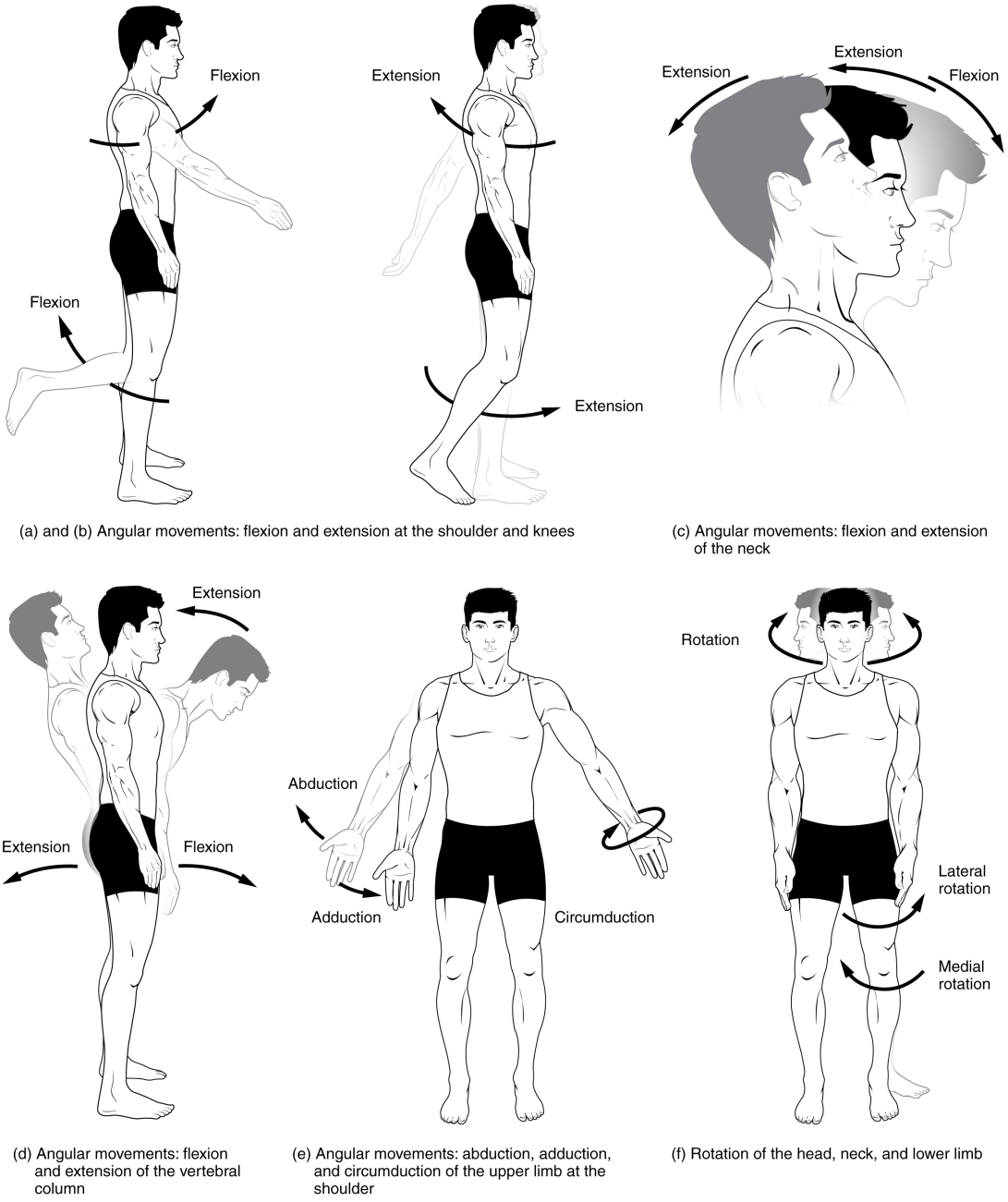


FIGURE 9.12 Movements of the Body, Part 1 Synovial joints give the body many ways in which to move. (a)–(b) Flexion and extension motions are in the sagittal (anterior–posterior) plane of motion. These movements take place at the shoulder, hip, elbow, knee, wrist, metacarpophalangeal, metatarsophalangeal, and interphalangeal joints. (c)–(d) Anterior bending of the head or vertebral column is flexion, while any posterior-going movement is extension. (e) Abduction and adduction are motions of the limbs, hand, fingers, or toes in the coronal (medial–lateral) plane of movement. Moving the limb or hand laterally away from the body, or spreading the fingers or toes, is abduction. Adduction brings the limb or hand toward or across the midline of the body, or brings the fingers or toes together. Circumduction is the movement of the limb, hand, or fingers in a circular pattern, using the sequential combination of flexion, adduction, extension, and abduction motions. Adduction/abduction and circumduction take place at the shoulder, hip, wrist, metacarpophalangeal, and metatarsophalangeal joints. (f) Turning of the head side to side or twisting of the body is rotation. Medial and lateral rotation of the upper limb at the shoulder or lower limb at the hip involves turning the anterior surface of the limb toward the midline of the body (medial or

elbow, the hand at the wrist, and the fingers at the metacarpophalangeal and interphalangeal joints. For the thumb, extension moves the thumb away from the palm of the hand, within the same plane as the palm, while flexion brings the thumb back against the index finger or into the palm. These motions take place at the first carpometacarpal joint. In the lower limb, bringing the thigh forward and upward is flexion at the hip joint, while any posterior-going motion of the thigh is extension. Note that extension of the thigh beyond the anatomical (standing) position is greatly limited by the ligaments that support the hip joint. Knee flexion is the bending of the knee to bring the foot toward the posterior thigh, and extension is the straightening of the knee. Flexion and extension movements are seen at the hinge, condyloid, saddle, and ball-and-socket joints of the limbs (see Figure 9.12**a-d**).

Hyperextension is the abnormal or excessive extension of a joint beyond its normal range of motion, thus resulting in injury. Similarly, **hyperflexion** is excessive flexion at a joint. Hyperextension injuries are common at hinge joints such as the knee or elbow. In cases of "whiplash" in which the head is suddenly moved backward and then forward, a patient may experience both hyperextension and hyperflexion of the cervical region.

Abduction and Adduction

Abduction and **adduction** motions occur within the coronal plane and involve medial-lateral motions of the limbs, fingers, toes, or thumb. Abduction moves the limb laterally away from the midline of the body, while adduction is the opposing movement that brings the limb toward the body or across the midline. For example, abduction is raising the arm at the shoulder joint, moving it laterally away from the body, while adduction brings the arm down to the side of the body. Similarly, abduction and adduction at the wrist moves the hand away from or toward the midline of the body. Spreading the fingers or toes apart is also abduction, while bringing the fingers or toes together is adduction. For the thumb, abduction is the anterior movement that brings the thumb to a 90° perpendicular position, pointing straight out from the palm. Adduction moves the thumb back to the anatomical position, next to the index finger. Abduction and adduction movements are seen at condyloid, saddle, and ball-and-socket joints (see Figure 9.12**e**).

Circumduction

Circumduction is the movement of a body region in a circular manner, in which one end of the body region being moved stays relatively stationary while the other end describes a circle. It involves the sequential combination of flexion, adduction, extension, and abduction at a joint. This type of motion is found at biaxial condyloid and saddle joints, and at multiaxial ball-and-sockets joints (see Figure 9.12**e**).

Rotation

Rotation can occur within the vertebral column, at a pivot joint, or at a ball-and-socket joint. Rotation of the neck or body is the twisting movement produced by the summation of the small rotational movements available between adjacent vertebrae. At a pivot joint, one bone rotates in relation to another bone. This is a uniaxial joint, and thus rotation is the only motion allowed at a pivot joint. For example, at the atlantoaxial joint, the first cervical (C1) vertebra (atlas) rotates around the dens, the upward projection from the second cervical (C2) vertebra (axis). This allows the head to rotate from side to side as when shaking the head "no." The proximal radioulnar joint is a pivot joint formed by the head of the radius and its articulation with the ulna. This joint allows for the radius to rotate along its length during pronation and supination movements of the forearm.

Rotation can also occur at the ball-and-socket joints of the shoulder and hip. Here, the humerus and femur rotate around their long axis, which moves the anterior surface of the arm or thigh either toward or away from the midline of the body. Movement that brings the anterior surface of the limb toward the midline of the body is called **medial (internal) rotation**. Conversely, rotation of the limb so that the anterior surface moves away from the midline is **lateral (external) rotation** (see Figure 9.12**f**). Be sure to distinguish medial and lateral rotation, which can only occur at the multiaxial shoulder and hip joints, from circumduction, which can occur at either biaxial or multiaxial joints.

Supination and Pronation

Supination and pronation are movements of the forearm. In the anatomical position, the upper limb is held next to the body with the palm facing forward. This is the **supinated position** of the forearm. In this position, the radius and ulna are parallel to each other. When the palm of the hand faces backward, the forearm is in the **pronated position**,

when carrying a heavy load with your hand or on your shoulder. You can feel this rotation when you pick up a load, such as a heavy book bag and carry it on only one shoulder. To increase its weight-bearing support for the bag, the shoulder lifts as the scapula superiorly rotates. **Inferior rotation** occurs during limb adduction and involves the downward motion of the glenoid cavity with upward movement of the medial end of the scapular spine.

Opposition and Reposition

Opposition is the thumb movement that brings the tip of the thumb in contact with the tip of a finger. This movement is produced at the first carpometacarpal joint, which is a saddle joint formed between the trapezium carpal bone and the first metacarpal bone. Thumb opposition is produced by a combination of flexion and abduction of the thumb at this joint. Returning the thumb to its anatomical position next to the index finger is called **reposition** (see Figure 9.13**l**).

Movements of the Joints

Type of Joint	Movement	Example
Pivot	Uniaxial joint; allows rotational movement	Atlantoaxial joint (C1–C2 vertebrae articulation); proximal radioulnar joint
Hinge	Uniaxial joint; allows flexion/extension movements	Knee; elbow; ankle; interphalangeal joints of fingers and toes
Condyloid	Biaxial joint; allows flexion/extension, abduction/adduction, and circumduction movements	Metacarpophalangeal (knuckle) joints of fingers; radiocarpal joint of wrist; metatarsophalangeal joints for toes
Saddle	Biaxial joint; allows flexion/extension, abduction/adduction, and circumduction movements	First carpometacarpal joint of the thumb; sternoclavicular joint
Plane	Multiaxial joint; allows inversion and eversion of foot, or flexion, extension, and lateral flexion of the vertebral column	Intertarsal joints of foot; superior-inferior articular process articulations between vertebrae
Ball-and-socket	Multiaxial joint; allows flexion/extension, abduction/adduction, circumduction, and medial/lateral rotation movements	Shoulder and hip joints

TABLE 9.1

9.6 Anatomy of Selected Synovial Joints

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the bones that articulate together to form selected synovial joints
- Discuss the movements available at each joint
- Describe the structures that support and prevent excess movements at each joint

Each synovial joint of the body is specialized to perform certain movements. The movements that are allowed are determined by the structural classification for each joint. For example, a multiaxial ball-and-socket joint has much more mobility than a uniaxial hinge joint. However, the ligaments and muscles that support a joint may place restrictions on the total range of motion available. Thus, the ball-and-socket joint of the shoulder has little in the way of ligament support, which gives the shoulder a very large range of motion. In contrast, movements at the hip joint are restricted by strong ligaments, which reduce its range of motion but confer stability during standing and

This joint involves the articulation between the mandibular fossa and articular tubercle of the temporal bone, with the condyle (head) of the mandible. Located between these bony structures, filling the gap between the skull and mandible, is a flexible articular disc (Figure 9.15). This disc serves to smooth the movements between the temporal bone and mandibular condyle.

Movement at the TMJ during opening and closing of the mouth involves both gliding and hinge motions of the mandible. With the mouth closed, the mandibular condyle and articular disc are located within the mandibular fossa of the temporal bone. During opening of the mouth, the mandible hinges downward and at the same time is pulled anteriorly, causing both the condyle and the articular disc to glide forward from the mandibular fossa onto the downward projecting articular tubercle. The net result is a forward and downward motion of the condyle and mandibular depression. The temporomandibular joint is supported by an extrinsic ligament that anchors the mandible to the skull. This ligament spans the distance between the base of the skull and the lingula on the medial side of the mandibular ramus.

Dislocation of the TMJ may occur when opening the mouth too wide (such as when taking a large bite) or following a blow to the jaw, resulting in the mandibular condyle moving beyond (anterior to) the articular tubercle. In this case, the individual would not be able to close their mouth. Temporomandibular joint disorder is a painful condition that may arise due to arthritis, wearing of the articular cartilage covering the bony surfaces of the joint, muscle fatigue from overuse or grinding of the teeth, damage to the articular disc within the joint, or jaw injury. Temporomandibular joint disorders can also cause headache, difficulty chewing, or even the inability to move the jaw (lock jaw). Pharmacologic agents for pain or other therapies, including bite guards, are used as treatments.

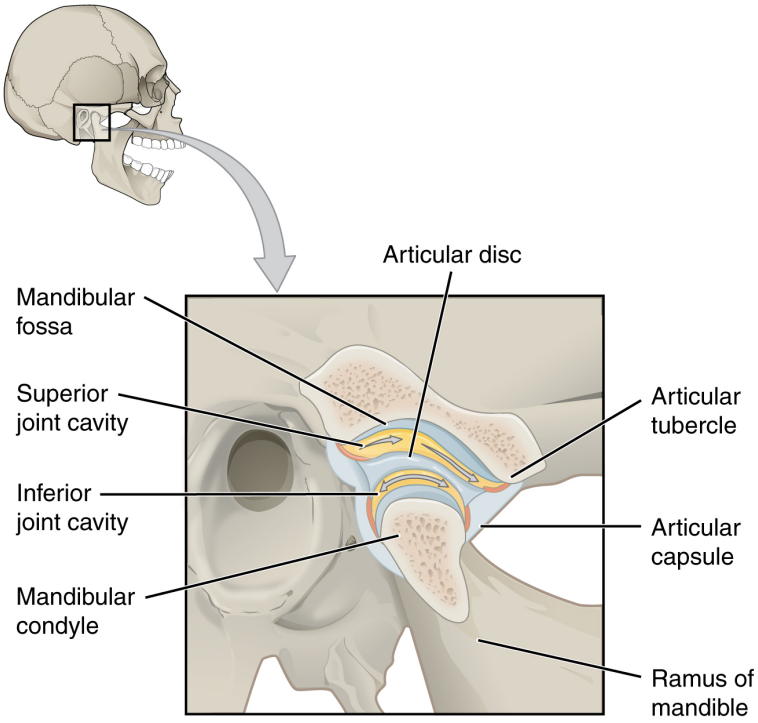


FIGURE 9.15 Temporomandibular Joint The temporomandibular joint is the articulation between the temporal bone of the skull and the condyle of the mandible, with an articular disc located between these bones. During depression of the mandible (opening of the mouth), the mandibular condyle moves both forward and hinges downward as it travels from the mandibular fossa onto the articular tubercle.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/TMJ) to learn about TMJ. Opening of the mouth requires the combination of two motions at the temporomandibular joint, an anterior gliding motion of the articular disc and mandible and the downward hinging of the mandible. What is the initial movement of the mandible during opening and how much mouth opening does this produce?

fully abducted, as when diving to catch a baseball and landing on your hand or elbow. Inflammatory responses to any shoulder injury can lead to the formation of scar tissue between the articular capsule and surrounding structures, thus reducing shoulder mobility, a condition called adhesive capsulitis (“frozen shoulder”).

INTERACTIVE LINK

Watch this video (http://openstax.org/l/shoulderjoint1) for a tutorial on the anatomy of the shoulder joint. What movements are available at the shoulder joint?

INTERACTIVE LINK

Watch this video (http://openstax.org/l/shoulderjoint2) to learn more about the anatomy of the shoulder joint, including bones, joints, muscles, nerves, and blood vessels. What is the shape of the glenoid labrum in cross-section, and what is the importance of this shape?

Elbow Joint

The **elbow joint** is a uniaxial hinge joint formed by the **humeroulnar joint**, the articulation between the trochlea of the humerus and the trochlear notch of the ulna. Also associated with the elbow are the **humeroradial joint** and the proximal radioulnar joint. All three of these joints are enclosed within a single articular capsule (Figure 9.17).

The articular capsule of the elbow is thin on its anterior and posterior aspects, but is thickened along its outside margins by strong intrinsic ligaments. These ligaments prevent side-to-side movements and hyperextension. On the medial side is the triangular **ulnar collateral ligament**. This arises from the medial epicondyle of the humerus and attaches to the medial side of the proximal ulna. The strongest part of this ligament is the anterior portion, which resists hyperextension of the elbow. The ulnar collateral ligament may be injured by frequent, forceful extensions of the forearm, as is seen in baseball pitchers. Reconstructive surgical repair of this ligament is referred to as Tommy John surgery, named for the former major league pitcher who was the first person to have this treatment.

The lateral side of the elbow is supported by the **radial collateral ligament**. This arises from the lateral epicondyle of the humerus and then blends into the lateral side of the annular ligament. The **annular ligament** encircles the head of the radius. This ligament supports the head of the radius as it articulates with the radial notch of the ulna at the proximal radioulnar joint. This is a pivot joint that allows for rotation of the radius during supination and pronation of the forearm.

femur. The ligaments are tightened by extension at the hip, thus pulling the head of the femur tightly into the acetabulum when in the upright, standing position. Very little additional extension of the thigh is permitted beyond this vertical position. These ligaments thus stabilize the hip joint and allow you to maintain an upright standing position with only minimal muscle contraction. Inside of the articular capsule, the **ligament of the head of the femur** (ligamentum teres) spans between the acetabulum and femoral head. This intracapsular ligament is normally slack and does not provide any significant joint support, but it does provide a pathway for an important artery that supplies the head of the femur.

The hip is prone to osteoarthritis, and thus was the first joint for which a replacement prosthesis was developed. A common injury in elderly individuals, particularly those with weakened bones due to osteoporosis, is a "broken hip," which is actually a fracture of the femoral neck. This may result from a fall, or it may cause the fall. This can happen as one lower limb is taking a step and all of the body weight is placed on the other limb, causing the femoral neck to break and producing a fall. Any accompanying disruption of the blood supply to the femoral neck or head can lead to necrosis of these areas, resulting in bone and cartilage death. Femoral fractures usually require surgical treatment, after which the patient will need mobility assistance for a prolonged period, either from family members or in a long-term care facility. Consequentially, the associated health care costs of "broken hips" are substantial. In addition, hip fractures are associated with increased rates of morbidity (incidences of disease) and mortality (death). Surgery for a hip fracture followed by prolonged bed rest may lead to life-threatening complications, including pneumonia, infection of pressure ulcers (bedsores), and thrombophlebitis (deep vein thrombosis; blood clot formation) that can result in a pulmonary embolism (blood clot within the lung).

condyles of the tibia. All of these articulations are enclosed within a single articular capsule. The knee functions as a hinge joint, allowing flexion and extension of the leg. This action is generated by both rolling and gliding motions of the femur on the tibia. In addition, some rotation of the leg is available when the knee is flexed, but not when extended. The knee is well constructed for weight bearing in its extended position, but is vulnerable to injuries associated with hyperextension, twisting, or blows to the medial or lateral side of the joint, particularly while weight bearing.

At the femoropatellar joint, the patella slides vertically within a groove on the distal femur. The patella is a sesamoid bone incorporated into the tendon of the quadriceps femoris muscle, the large muscle of the anterior thigh. The patella serves to protect the quadriceps tendon from friction against the distal femur. Continuing from the patella to the anterior tibia just below the knee is the **patellar ligament**. Acting via the patella and patellar ligament, the quadriceps femoris is a powerful muscle that acts to extend the leg at the knee. It also serves as a "dynamic ligament" to provide very important support and stabilization for the knee joint.

The medial and lateral tibiofemoral joints are the articulations between the rounded condyles of the femur and the relatively flat condyles of the tibia. During flexion and extension motions, the condyles of the femur both roll and glide over the surfaces of the tibia. The rolling action produces flexion or extension, while the gliding action serves to maintain the femoral condyles centered over the tibial condyles, thus ensuring maximal bony, weight-bearing support for the femur in all knee positions. As the knee comes into full extension, the femur undergoes a slight medial rotation in relation to tibia. The rotation results because the lateral condyle of the femur is slightly smaller than the medial condyle. Thus, the lateral condyle finishes its rolling motion first, followed by the medial condyle. The resulting small medial rotation of the femur serves to "lock" the knee into its fully extended and most stable position. Flexion of the knee is initiated by a slight lateral rotation of the femur on the tibia, which "unlocks" the knee. This lateral rotation motion is produced by the popliteus muscle of the posterior leg.

Located between the articulating surfaces of the femur and tibia are two articular discs, the **medial meniscus** and **lateral meniscus** (see Figure 9.19**b**). Each is a C-shaped fibrocartilage structure that is thin along its inside margin and thick along the outer margin. They are attached to their tibial condyles, but do not attach to the femur. While both menisci are free to move during knee motions, the medial meniscus shows less movement because it is anchored at its outer margin to the articular capsule and tibial collateral ligament. The menisci provide padding between the bones and help to fill the gap between the round femoral condyles and flattened tibial condyles. Some areas of each meniscus lack an arterial blood supply and thus these areas heal poorly if damaged.

The knee joint has multiple ligaments that provide support, particularly in the extended position (see Figure 9.19**c**). Outside of the articular capsule, located at the sides of the knee, are two extrinsic ligaments. The **fibular collateral ligament** (lateral collateral ligament) is on the lateral side and spans from the lateral epicondyle of the femur to the head of the fibula. The **tibial collateral ligament** (medial collateral ligament) of the medial knee runs from the medial epicondyle of the femur to the medial tibia. As it crosses the knee, the tibial collateral ligament is firmly attached on its deep side to the articular capsule and to the medial meniscus, an important factor when considering knee injuries. In the fully extended knee position, both collateral ligaments are taut (tight), thus serving to stabilize and support the extended knee and preventing side-to-side or rotational motions between the femur and tibia.

The articular capsule of the posterior knee is thickened by intrinsic ligaments that help to resist knee hyperextension. Inside the knee are two intracapsular ligaments, the **anterior cruciate ligament** and **posterior cruciate ligament**. These ligaments are anchored inferiorly to the tibia at the intercondylar eminence, the roughened area between the tibial condyles. The cruciate ligaments are named for whether they are attached anteriorly or posteriorly to this tibial region. Each ligament runs diagonally upward to attach to the inner aspect of a femoral condyle. The cruciate ligaments are named for the X-shape formed as they pass each other (cruciate means "cross"). The posterior cruciate ligament is the stronger ligament. It serves to support the knee when it is flexed and weight bearing, as when walking downhill. In this position, the posterior cruciate ligament prevents the femur from sliding anteriorly off the top of the tibia. The anterior cruciate ligament becomes tight when the knee is extended, and thus resists hyperextension.

the tibia on the dashboard when not wearing a seatbelt during an automobile accident. More commonly, injuries occur when forces are applied to the extended knee, particularly when the foot is planted and unable to move. Anterior cruciate ligament injuries can result with a forceful blow to the anterior knee, producing hyperextension, or when a runner makes a quick change of direction that produces both twisting and hyperextension of the knee.

A worse combination of injuries can occur with a hit to the lateral side of the extended knee (Figure 9.20). A moderate blow to the lateral knee will cause the medial side of the joint to open, resulting in stretching or damage to the tibial collateral ligament. Because the medial meniscus is attached to the tibial collateral ligament, a stronger blow can tear the ligament and also damage the medial meniscus. This is one reason that the medial meniscus is 20 times more likely to be injured than the lateral meniscus. A powerful blow to the lateral knee produces a "terrible triad" injury, in which there is a sequential injury to the tibial collateral ligament, medial meniscus, and anterior cruciate ligament.

Arthroscopic surgery has greatly improved the surgical treatment of knee injuries and reduced subsequent recovery times. This procedure involves a small incision and the insertion into the joint of an arthroscope, a pencil-thin instrument that allows for visualization of the joint interior. Small surgical instruments are also inserted via additional incisions. These tools allow a surgeon to remove or repair a torn meniscus or to reconstruct a ruptured cruciate ligament. The current method for anterior cruciate ligament replacement involves using a portion of the patellar ligament. Holes are drilled into the cruciate ligament attachment points on the tibia and femur, and the patellar ligament graft, with small areas of attached bone still intact at each end, is inserted into these holes. The bone-to-bone sites at each end of the graft heal rapidly and strongly, thus enabling a rapid recovery.

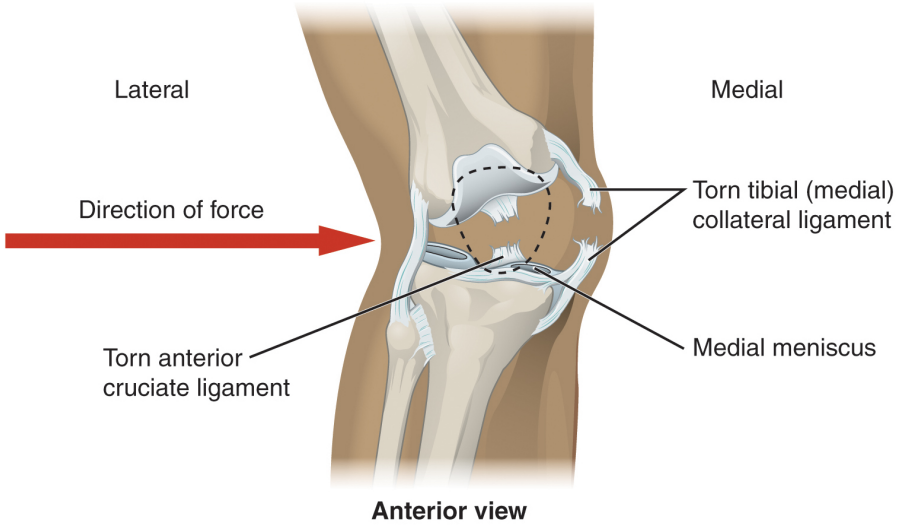


FIGURE 9.20 Knee Injury A strong blow to the lateral side of the extended knee will cause three injuries, in sequence: tearing of the tibial collateral ligament, damage to the medial meniscus, and rupture of the anterior cruciate ligament.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/kneeinjury) to learn more about different knee injuries and diagnostic testing of the knee. What are the most common causes of anterior cruciate ligament injury?

Ankle and Foot Joints

The ankle is formed by the **talocrural joint** (Figure 9.21). It consists of the articulations between the talus bone of the foot and the distal ends of the tibia and fibula of the leg (crural = "leg"). The superior aspect of the talus bone is square-shaped and has three areas of articulation. The top of the talus articulates with the inferior tibia. This is the portion of the ankle joint that carries the body weight between the leg and foot. The sides of the talus are firmly held in position by the articulations with the medial malleolus of the tibia and the lateral malleolus of the fibula, which

INTERACTIVE LINK

Watch this video (http://openstax.org/l/anklejoint2) to learn more about the anatomy of the ankle joint, including bones, joints, muscles, nerves, and blood vessels. Which type of joint used in woodworking does the ankle joint resemble?

Disorders of the...

Joints

The ankle is the most frequently injured joint in the body, with the most common injury being an inversion ankle sprain. A sprain is the stretching or tearing of the supporting ligaments. Excess inversion causes the talus bone to tilt laterally, thus damaging the ligaments on the lateral side of the ankle. The anterior talofibular ligament is most commonly injured, followed by the calcaneofibular ligament. In severe inversion injuries, the forceful lateral movement of the talus not only ruptures the lateral ankle ligaments, but also fractures the distal fibula.

Less common are eversion sprains of the ankle, which involve stretching of the deltoid ligament on the medial side of the ankle. Forcible eversion of the foot, for example, with an awkward landing from a jump or when a football player has a foot planted and is hit on the lateral ankle, can result in a Pott's fracture and dislocation of the ankle joint. In this injury, the very strong deltoid ligament does not tear, but instead shears off the medial malleolus of the tibia. This frees the talus, which moves laterally and fractures the distal fibula. In extreme cases, the posterior margin of the tibia may also be sheared off.

Above the ankle, the distal ends of the tibia and fibula are united by a strong syndesmosis formed by the interosseous membrane and ligaments at the distal tibiofibular joint. These connections prevent separation between the distal ends of the tibia and fibula and maintain the talus locked into position between the medial malleolus and lateral malleolus. Injuries that produce a lateral twisting of the leg on top of the planted foot can result in stretching or tearing of the tibiofibular ligaments, producing a syndesmotic ankle sprain or "high ankle sprain."

Most ankle sprains can be treated using the RICE technique: Rest, Ice, Compression, and Elevation. Reducing joint mobility using a brace or cast may be required for a period of time. More severe injuries involving ligament tears or bone fractures may require surgery.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/anklejoint3) to learn more about the ligaments of the ankle joint, ankle sprains, and treatment. During an inversion ankle sprain injury, all three ligaments that resist excessive inversion of the foot may be injured. What is the sequence in which these three ligaments are injured?

9.7 Development of Joints

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the two processes by which mesenchyme can give rise to bone
- Discuss the process by which joints of the limbs are formed

Joints form during embryonic development in conjunction with the formation and growth of the associated bones. The embryonic tissue that gives rise to all bones, cartilages, and connective tissues of the body is called mesenchyme. In the head, mesenchyme will accumulate at those areas that will become the bones that form the top and sides of the skull. The mesenchyme in these areas will develop directly into bone through the process of intramembranous ossification, in which mesenchymal cells differentiate into bone-producing cells that then generate bone tissue. The mesenchyme between the areas of bone production will become the fibrous connective tissue that fills the spaces between the developing bones. Initially, the connective tissue-filled gaps between the bones are wide, and are called fontanelles. After birth, as the skull bones grow and enlarge, the gaps between them decrease in width and the fontanelles are reduced to suture joints in which the bones are united by a narrow layer of

Key Terms

abduction movement in the coronal plane that moves a limb laterally away from the body; spreading of the fingers

acetabular labrum lip of fibrocartilage that surrounds outer margin of the acetabulum on the hip bone

adduction movement in the coronal plane that moves a limb medially toward or across the midline of the body; bringing fingers together

amphiarthrosis slightly mobile joint

annular ligament intrinsic ligament of the elbow articular capsule that surrounds and supports the head of the radius at the proximal radioulnar joint

anterior cruciate ligament intracapsular ligament of the knee; extends from anterior, superior surface of the tibia to the inner aspect of the lateral condyle of the femur; resists hyperextension of knee

anterior talofibular ligament intrinsic ligament located on the lateral side of the ankle joint, between talus bone and lateral malleolus of fibula; supports talus at the talocrural joint and resists excess inversion of the foot

articular capsule connective tissue structure that encloses the joint cavity of a synovial joint

articular cartilage thin layer of hyaline cartilage that covers the articulating surfaces of bones at a synovial joint

articular disc meniscus; a fibrocartilage structure found between the bones of some synovial joints; provides padding or smooths movements between the bones; strongly unites the bones together

articulation joint of the body

atlanto-occipital joint articulation between the occipital condyles of the skull and the superior articular processes of the atlas (C1 vertebra)

atlantoaxial joint series of three articulations between the atlas (C1) vertebra and the axis (C2) vertebra, consisting of the joints between the inferior articular processes of C1 and the superior articular processes of C2, and the articulation between the dens of C2 and the anterior arch of C1

ball-and-socket joint synovial joint formed between the spherical end of one bone (the ball) that fits into the depression of a second bone (the socket); found at the hip and shoulder joints; functionally classified as a multiaxial joint

biaxial joint type of diarthrosis; a joint that allows for movements within two planes (two axes)

bursa connective tissue sac containing lubricating fluid that prevents friction between adjacent structures, such as skin and bone, tendons and bone, or between muscles

calcaneofibular ligament intrinsic ligament located on the lateral side of the ankle joint, between the calcaneus bone and lateral malleolus of the fibula; supports the talus bone at the ankle joint and resists excess inversion of the foot

cartilaginous joint joint at which the bones are united by hyaline cartilage (synchondrosis) or fibrocartilage (symphysis)

circumduction circular motion of the arm, thigh, hand, thumb, or finger that is produced by the sequential combination of flexion, abduction, extension, and adduction

condyloid joint synovial joint in which the shallow depression at the end of one bone receives a rounded end from a second bone or a rounded structure formed by two bones; found at the metacarpophalangeal joints of the fingers or the radiocarpal joint of the wrist; functionally classified as a biaxial joint

coracohumeral ligament intrinsic ligament of the shoulder joint; runs from the coracoid process of the scapula to the anterior humerus

deltoid ligament broad intrinsic ligament located on the medial side of the ankle joint; supports the talus at the talocrural joint and resists excess eversion of the foot

depression downward (inferior) motion of the scapula or mandible

diarthrosis freely mobile joint

dorsiflexion movement at the ankle that brings the top of the foot toward the anterior leg

elbow joint humeroulnar joint

elevation upward (superior) motion of the scapula or mandible

eversion foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned laterally, away from the midline

extension movement in the sagittal plane that increases the angle of a joint (straightens the joint); motion involving posterior bending of the vertebral column or returning to the upright position from a flexed position

extrinsic ligament ligament located outside of the articular capsule of a synovial joint

femoropatellar joint portion of the knee joint consisting of the articulation between the distal femur and the patella

fibrous joint joint where the articulating areas of the adjacent bones are connected by fibrous connective tissue

fibular collateral ligament extrinsic ligament of the knee joint that spans from the lateral epicondyle of

meniscus articular disc
multiaxial joint type of diarthrosis; a joint that allows for movements within three planes (three axes)
opposition thumb movement that brings the tip of the thumb in contact with the tip of a finger
patellar ligament ligament spanning from the patella to the anterior tibia; serves as the final attachment for the quadriceps femoris muscle
periodontal ligament band of dense connective tissue that anchors the root of a tooth into the bony jaw socket
pivot joint synovial joint at which the rounded portion of a bone rotates within a ring formed by a ligament and an articulating bone; functionally classified as uniaxial joint
plane joint synovial joint formed between the flattened articulating surfaces of adjacent bones; functionally classified as a multiaxial joint
plantar flexion foot movement at the ankle in which the heel is lifted off of the ground
posterior cruciate ligament intracapsular ligament of the knee; extends from the posterior, superior surface of the tibia to the inner aspect of the medial condyle of the femur; prevents anterior displacement of the femur when the knee is flexed and weight bearing
posterior talofibular ligament intrinsic ligament located on the lateral side of the ankle joint, between the talus bone and lateral malleolus of the fibula; supports the talus at the talocrural joint and resists excess inversion of the foot
pronated position forearm position in which the palm faces backward
pronation forearm motion that moves the palm of the hand from the palm forward to the palm backward position
protraction anterior motion of the scapula or mandible
proximal radioulnar joint articulation between head of radius and radial notch of ulna; uniaxial pivot joint that allows for rotation of radius during pronation/supination of forearm
pubofemoral ligament intrinsic ligament spanning from the pubis of the hip bone to the femur, on the anterior-inferior aspect of the hip joint
radial collateral ligament intrinsic ligament on the lateral side of the elbow joint; runs from the lateral epicondyle of humerus to merge with the annular ligament
reposition movement of the thumb from opposition back to the anatomical position (next to index finger)
retraction posterior motion of the scapula or mandible
rotation movement of a bone around a central axis (atlantoaxial joint) or around its long axis (proximal radioulnar joint; shoulder or hip joint); twisting of the vertebral column resulting from the summation of small motions between adjacent vertebrae
rotator cuff strong connective tissue structure formed by the fusion of four rotator cuff muscle tendons to the articular capsule of the shoulder joint; surrounds and supports superior, anterior, lateral, and posterior sides of the humeral head
saddle joint synovial joint in which the articulating ends of both bones are convex and concave in shape, such as at the first carpometacarpal joint at the base of the thumb; functionally classified as a biaxial joint
subacromial bursa bursa that protects the supraspinatus muscle tendon and superior end of the humerus from rubbing against the acromion of the scapula
subcutaneous bursa bursa that prevents friction between skin and an underlying bone
submuscular bursa bursa that prevents friction between bone and a muscle or between adjacent muscles
subscapular bursa bursa that prevents rubbing of the subscapularis muscle tendon against the scapula
subtalar joint articulation between the talus and calcaneus bones of the foot; allows motions that contribute to inversion/eversion of the foot
subtendinous bursa bursa that prevents friction between bone and a muscle tendon
superior rotation movement of the scapula during upper limb abduction in which the glenoid cavity of the scapula moves in an upward direction as the medial end of the scapular spine moves in a downward direction
supinated position forearm position in which the palm faces anteriorly (anatomical position)
supination forearm motion that moves the palm of the hand from the palm backward to the palm forward position
suture fibrous joint that connects the bones of the skull (except the mandible); an immobile joint (synarthrosis)
symphysis type of cartilaginous joint where the bones are joined by fibrocartilage
synarthrosis immobile or nearly immobile joint
synchondrosis type of cartilaginous joint where the bones are joined by hyaline cartilage
syndesmosis type of fibrous joint in which two separated, parallel bones are connected by an

9.3 Cartilaginous Joints

There are two types of cartilaginous joints. A synchondrosis is formed when the adjacent bones are united by hyaline cartilage. A temporary synchondrosis is formed by the epiphyseal plate of a growing long bone, which is lost when the epiphyseal plate ossifies as the bone reaches maturity. The synchondrosis is thus replaced by a synostosis. Permanent synchondroses that do not ossify are found at the first sternocostal joint and between the anterior ends of the bony ribs and the junction with their costal cartilage. A symphysis is where the bones are joined by fibrocartilage and the gap between the bones may be narrow or wide. A narrow symphysis is found at the manubriosternal joint and at the pubic symphysis. A wide symphysis is the intervertebral symphysis in which the bodies of adjacent vertebrae are united by an intervertebral disc.

9.4 Synovial Joints

Synovial joints are the most common type of joints in the body. They are characterized by the presence of a joint cavity, inside of which the bones of the joint articulate with each other. The articulating surfaces of the bones at a synovial joint are not directly connected to each other by connective tissue or cartilage, which allows the bones to move freely against each other. The walls of the joint cavity are formed by the articular capsule. Friction between the bones is reduced by a thin layer of articular cartilage covering the surfaces of the bones, and by a lubricating synovial fluid, which is secreted by the synovial membrane.

Synovial joints are strengthened by the presence of ligaments, which hold the bones together and resist excessive or abnormal movements of the joint. Ligaments are classified as extrinsic ligaments if they are located outside of the articular capsule, intrinsic ligaments if they are fused to the wall of the articular capsule, or intracapsular ligaments if they are located inside the articular capsule. Some synovial joints also have an articular disc (meniscus), which can provide padding between the bones, smooth their movements, or strongly join the bones together to strengthen the joint. Muscles and their tendons acting across a joint can also increase their contractile strength when needed, thus providing indirect support for the joint.

Bursae contain a lubricating fluid that serves to reduce friction between structures. Subcutaneous bursae prevent friction between the skin and an underlying bone, submuscular bursae protect muscles from rubbing against a bone or another muscle, and a subtendinous bursa prevents friction between bone and a muscle tendon. Tendon sheaths contain a lubricating fluid and surround tendons to allow for smooth movement of the tendon as it crosses a joint.

Based on the shape of the articulating bone surfaces and the types of movement allowed, synovial joints are classified into six types. At a pivot joint, one bone is held within a ring by a ligament and its articulation with a second bone. Pivot joints only allow for rotation around a single axis. These are found at the articulation between the C1 (atlas) and the dens of the C2 (axis) vertebrae, which provides the side-to-side rotation of the head, or at the proximal radioulnar joint between the head of the radius and the radial notch of the ulna, which allows for rotation of the radius during forearm movements. Hinge joints, such as at the elbow, knee, ankle, or interphalangeal joints between phalanx bones of the fingers and toes, allow only for bending and straightening of the joint. Pivot and hinge joints are functionally classified as uniaxial joints.

Condyloid joints are found where the shallow depression of one bone receives a rounded bony area formed by one or two bones. Condyloid joints are found at the base of the fingers (metacarpophalangeal joints) and at the wrist (radiocarpal joint). At a saddle joint, the articulating bones fit together like a rider and a saddle. An example is the first carpometacarpal joint located at the base of the thumb. Both condyloid and saddle joints are functionally classified as biaxial joints.

Plane joints are formed between the small, flattened surfaces of adjacent bones. These joints allow the bones to slide or rotate against each other, but the range of motion is usually slight and tightly limited by ligaments or surrounding bones. This type of joint is found between the articular processes of adjacent vertebrae, at the acromioclavicular joint, or at the intercarpal joints of the hand and intertarsal joints of the foot. Ball-and-socket joints, in which the rounded head of a bone fits into a large depression or socket, are found at the shoulder and hip joints. Both plane and ball-and-sockets joints are classified functionally as multiaxial joints. However, ball-and-socket joints allow for large movements, while the motions between bones at a plane joint are small.

9.5 Types of Body Movements

The variety of movements provided by the different types of synovial joints allows for a large range of body motions and gives you tremendous mobility. These movements allow you to flex or extend your body or limbs, medially rotate and adduct your arms and flex your elbows to hold a heavy object against your chest, raise your arms above your head, rotate or shake your

movements. The medial and lateral tibiofemoral joints, between the condyles of the femur and condyles of the tibia, are modified hinge joints that allow for knee extension and flexion. During these movements, the condyles of the femur both roll and glide over the surface of the tibia. As the knee comes into full extension, a slight medial rotation of the femur serves to "lock" the knee into its most stable, weight-bearing position. The reverse motion, a small lateral rotation of the femur, is required to initiate knee flexion. When the knee is flexed, some rotation of the leg is available.

Two extrinsic ligaments, the tibial collateral ligament on the medial side and the fibular collateral ligament on the lateral side, serve to resist hyperextension or rotation of the extended knee joint. Two intracapsular ligaments, the anterior cruciate ligament and posterior cruciate ligament, span between the tibia and the inner aspects of the femoral condyles. The anterior cruciate ligament resists hyperextension of the knee, while the posterior cruciate ligament prevents anterior sliding of the femur, thus supporting the knee when it is flexed and weight bearing. The medial and lateral menisci, located between the femoral and tibial condyles, are articular discs that provide padding and improve the fit between the bones.

The talocrural joint forms the ankle. It consists of the articulation between the talus bone and the medial malleolus of the tibia, the distal end of the tibia, and the lateral malleolus of the fibula. This is a uniaxial hinge joint that allows only dorsiflexion and plantar flexion of the foot. Gliding motions at the subtalar and intertarsal joints of the foot allow for inversion/eversion of the foot. The ankle joint is supported on the medial side by the deltoid ligament, which prevents side-to-side motions of the talus at the talocrural joint and resists excessive eversion of the foot. The lateral ankle is supported by the anterior and posterior talofibular ligaments and the calcaneofibular ligament. These support the ankle joint and also resist excess inversion of the foot. An inversion ankle sprain, a common injury, will result in injury to one or more of these lateral ankle ligaments.

9.7 Development of Joints

During embryonic growth, bones and joints develop from mesenchyme, an embryonic tissue that gives rise to bone, cartilage, and fibrous connective tissues. In the skull, the bones develop either directly from mesenchyme through the process of intramembranous ossification, or indirectly through endochondral ossification, which initially forms a hyaline cartilage model of the future bone, which is later converted into bone. In both cases, the mesenchyme between the developing bones differentiates into fibrous connective tissue that will unite the skull bones at suture joints. In the limbs, mesenchyme accumulations within the growing limb bud will become a hyaline cartilage model for each of the limb bones. A joint interzone will develop between these areas of cartilage. Mesenchyme cells at the margins of the interzone will give rise to the articular capsule, while cell death at the center forms the space that will become the joint cavity of the future synovial joint. The hyaline cartilage model of each limb bone will eventually be converted into bone via the process of endochondral ossification. However, hyaline cartilage will remain, covering the ends of the adult bone as the articular cartilage.

Interactive Link Questions

1. Go to this website (http://openstax.org/l/childhand) to view a radiograph (X-ray image) of a child's hand and wrist. The growing bones of child have an epiphyseal plate that forms a synchondrosis between the shaft and end of a long bone. Being less dense than bone, the area of epiphyseal cartilage is seen on this radiograph as the dark epiphyseal gaps located near the ends of the long bones, including the radius, ulna, metacarpal, and phalanx bones. Which of the bones in this image do not show an epiphyseal plate (epiphyseal gap)?

2. Watch this video (http://openstax.org/l/synjoints) to see an animation of synovial joints in action. Synovial joints are places where bones articulate with each other inside of a joint cavity. The different types of synovial joints are the ball-and-socket joint (shoulder joint), hinge joint (knee), pivot joint (atlantoaxial joint, between C1 and C2 vertebrae of the neck), condyloid joint (radiocarpal joint of the wrist), saddle joint (first carpometacarpal joint, between the trapezium carpal bone and the first metacarpal bone, at the base of the thumb), and plane joint (facet joints of vertebral column, between superior and inferior articular processes). Which type of synovial joint allows for the widest ranges of motion?

Review Questions

20. The joint between adjacent vertebrae that includes an invertebral disc is classified as which type of joint?
a. diarthrosis
b. multiaxial
c. amphiarthrosis
d. synarthrosis

21. Which of these joints is classified as a synarthrosis?
a. the pubic symphysis
b. the manubriosternal joint
c. an invertebral disc
d. the shoulder joint

22. Which of these joints is classified as a biaxial diarthrosis?
a. the metacarpophalangeal joint
b. the hip joint
c. the elbow joint
d. the pubic symphysis

23. Synovial joints _____.
a. may be functionally classified as a synarthrosis
b. are joints where the bones are connected to each other by hyaline cartilage
c. may be functionally classified as an amphiarthrosis
d. are joints where the bones articulate with each other within a fluid-filled joint cavity

24. Which type of fibrous joint connects the tibia and fibula?
a. syndesmosis
b. symphysis
c. suture
d. gomphosis

25. An example of a wide fibrous joint is _____.
a. the interosseous membrane of the forearm
b. a gomphosis
c. a suture joint
d. a synostosis

26. A gomphosis _____.
a. is formed by an interosseous membrane
b. connects the tibia and fibula bones of the leg
c. contains a joint cavity
d. anchors a tooth to the jaw

27. A syndesmosis is _____.
a. a narrow fibrous joint
b. the type of joint that unites bones of the skull
c. a fibrous joint that unites parallel bones
d. the type of joint that anchors the teeth in the jaws

28. A cartilaginous joint _____.
a. has a joint cavity
b. is called a symphysis when the bones are united by fibrocartilage
c. anchors the teeth to the jaws
d. is formed by a wide sheet of fibrous connective tissue

29. A synchondrosis is _____.
a. found at the pubic symphysis
b. where bones are connected together with fibrocartilage
c. a type of fibrous joint
d. found at the first sternocostal joint of the thoracic cage

30. Which of the following are joined by a symphysis?
a. adjacent vertebrae
b. the first rib and the sternum
c. the end and shaft of a long bone
d. the radius and ulna bones

31. The epiphyseal plate of a growing long bone in a child is classified as a _____.
a. synchondrosis
b. synostosis
c. symphysis
d. syndesmosis

32. Which type of joint provides the greatest range of motion?
a. ball-and-socket
b. hinge
c. condyloid
d. plane

33. Which type of joint allows for only uniaxial movement?
a. saddle joint
b. hinge joint
c. condyloid joint
d. ball-and-socket joint

34. Which of the following is a type of synovial joint?
a. a synostosis
b. a suture
c. a plane joint
d. a synchondrosis

47. Which statement is true concerning the knee joint?
   a. The lateral meniscus is an intrinsic ligament located on the lateral side of the knee joint.
   b. Hyperextension is resisted by the posterior cruciate ligament.
   c. The anterior cruciate ligament supports the knee when it is flexed and weight bearing.
   d. The medial meniscus is attached to the tibial collateral ligament.

48. The ankle joint _____.
   a. is also called the subtalar joint
   b. allows for gliding movements that produce inversion/eversion of the foot
   c. is a uniaxial hinge joint
   d. is supported by the tibial collateral ligament on the lateral side

49. Which region of the vertebral column has the *greatest* range of motion for rotation?
   a. cervical
   b. thoracic
   c. lumbar
   d. sacral

50. Intramembranous ossification _____.
   a. gives rise to the bones of the limbs
   b. produces the bones of the top and sides of the skull
   c. produces the bones of the face and base of the skull
   d. involves the conversion of a hyaline cartilage model into bone

51. Synovial joints _____.
   a. are derived from fontanelles
   b. are produced by intramembranous ossification
   c. develop at an interzone site
   d. are produced by endochondral ossification

52. Endochondral ossification is _____.
   a. the process that replaces hyaline cartilage with bone tissue
   b. the process by which mesenchyme differentiates directly into bone tissue
   c. completed before birth
   d. the process that gives rise to the joint interzone and future joint cavity

Critical Thinking Questions

53. Define how joints are classified based on function. Describe and give an example for each functional type of joint.

54. Explain the reasons for why joints differ in their degree of mobility.

55. Distinguish between a narrow and wide fibrous joint and give an example of each.

56. The periodontal ligaments are made of collagen fibers and are responsible for connecting the roots of the teeth to the jaws. Describe how scurvy, a disease that inhibits collagen production, can affect the teeth.

57. Describe the two types of cartilaginous joints and give examples of each.

58. Both functional and structural classifications can be used to describe an individual joint. Define the first sternocostal joint and the pubic symphysis using both functional and structural characteristics.

59. Describe the characteristic structures found at all synovial joints.

60. Describe the structures that provide direct and indirect support for a synovial joint.

61. Briefly define the types of joint movements available at a ball-and-socket joint.

62. Discuss the joints involved and movements required for you to cross your arms together in front of your chest.

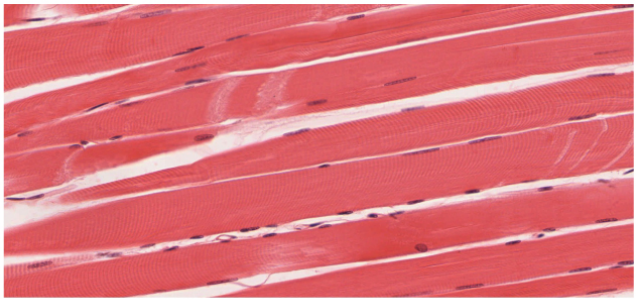
63. Discuss the structures that contribute to support of the shoulder joint.

64. Describe the sequence of injuries that may occur if the extended, weight-bearing knee receives a very strong blow to the lateral side of the knee.

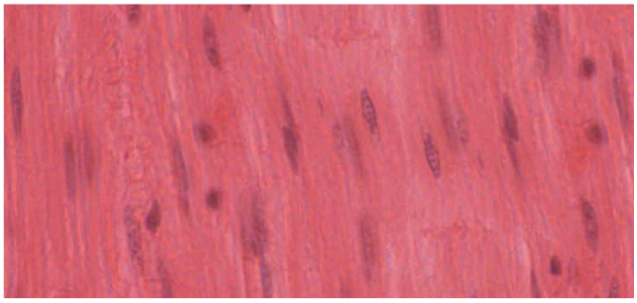
65. Describe how synovial joints develop within the embryonic limb.

66. Differentiate between endochondral and intramembranous ossification.

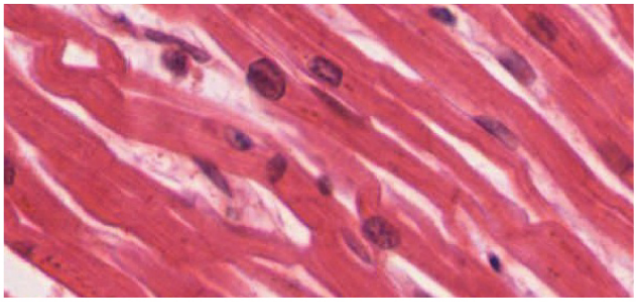
(from polarized to depolarized) and send an electrical wave called an action potential along the entire length of the membrane. While the nervous system can influence the excitability of cardiac and smooth muscle to some degree, skeletal muscle completely depends on signaling from the nervous system to work properly. On the other hand, both cardiac muscle and smooth muscle can respond to other stimuli, such as hormones and local stimuli.



(a)



(b)



(c)

FIGURE 10.2 The Three Types of Muscle Tissue The body contains three types of muscle tissue: (a) skeletal muscle, (b) smooth muscle, and (c) cardiac muscle. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The muscles all begin the actual process of contracting (shortening) when a protein called actin is pulled by a protein called myosin. This occurs in striated muscle (skeletal and cardiac) after specific binding sites on the actin have been exposed in response to the interaction between calcium ions (Ca^{++}) and proteins (troponin and tropomyosin) that "shield" the actin-binding sites. Ca^{++} also is required for the contraction of smooth muscle, although its role is different: here Ca^{++} activates enzymes, which in turn activate myosin heads. All muscles require adenosine triphosphate (ATP) to continue the process of contracting, and they all relax when the Ca^{++} is removed and the actin-binding sites are re-shielded.

A muscle can return to its original length when relaxed due to a quality of muscle tissue called **elasticity**. It can recoil back to its original length due to elastic fibers. Muscle tissue also has the quality of **extensibility**; it can stretch or extend. **Contractility** allows muscle tissue to pull on its attachment points and shorten with force.

Differences among the three muscle types include the microscopic organization of their contractile proteins—actin and myosin. The actin and myosin proteins are arranged very regularly in the cytoplasm of individual muscle cells (referred to as fibers) in both skeletal muscle and cardiac muscle, which creates a pattern, or stripes, called striations. The striations are visible with a light microscope under high magnification (see Figure 10.2). **Skeletal**

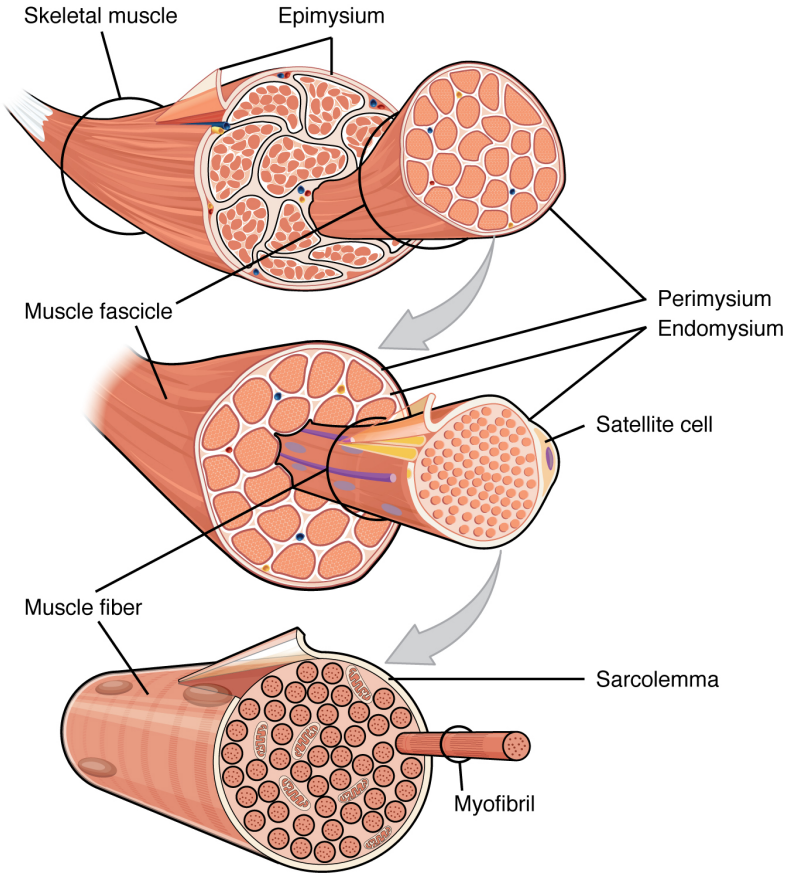


FIGURE 10.3 The Three Connective Tissue Layers Bundles of muscle fibers, called fascicles, are covered by the perimysium. Muscle fibers are covered by the endomysium.

Inside each skeletal muscle, muscle fibers are organized into individual bundles, each called a **fascicle**, by a middle layer of connective tissue called the **perimysium**. This fascicular organization is common in muscles of the limbs; it allows the nervous system to trigger a specific movement of a muscle by activating a subset of muscle fibers within a bundle, or fascicle of the muscle. Inside each fascicle, each muscle fiber is encased in a thin connective tissue layer of collagen and reticular fibers called the **endomysium**. The endomysium contains the extracellular fluid and nutrients to support the muscle fiber. These nutrients are supplied via blood to the muscle tissue.

In skeletal muscles that work with tendons to pull on bones, the collagen in the three tissue layers (the mysia) intertwines with the collagen of a tendon. At the other end of the tendon, it fuses with the periosteum coating the bone. The tension created by contraction of the muscle fibers is then transferred though the mysia, to the tendon, and then to the periosteum to pull on the bone for movement of the skeleton. In other places, the mysia may fuse with a broad, tendon-like sheet called an **aponeurosis**, or to fascia, the connective tissue between skin and bones. The broad sheet of connective tissue in the lower back that the latissimus dorsi muscles (the “lats”) fuse into is an example of an aponeurosis.

Every skeletal muscle is also richly supplied by blood vessels for nourishment, oxygen delivery, and waste removal. In addition, every muscle fiber in a skeletal muscle is supplied by the axon branch of a somatic motor neuron, which signals the fiber to contract. Unlike cardiac and smooth muscle, the only way to functionally contract a skeletal muscle is through signaling from the nervous system.

Skeletal Muscle Fibers

Because skeletal muscle cells are long and cylindrical, they are commonly referred to as muscle fibers. Skeletal muscle fibers can be quite large for human cells, with diameters up to 100 μm and lengths up to 30 cm (11.8 in) in the Sartorius of the upper leg. During early development, embryonic myoblasts, each with its own nucleus, fuse with up to hundreds of other myoblasts to form the multinucleated skeletal muscle fibers. Multiple nuclei mean multiple copies of genes, permitting the production of the large amounts of proteins and enzymes needed for muscle

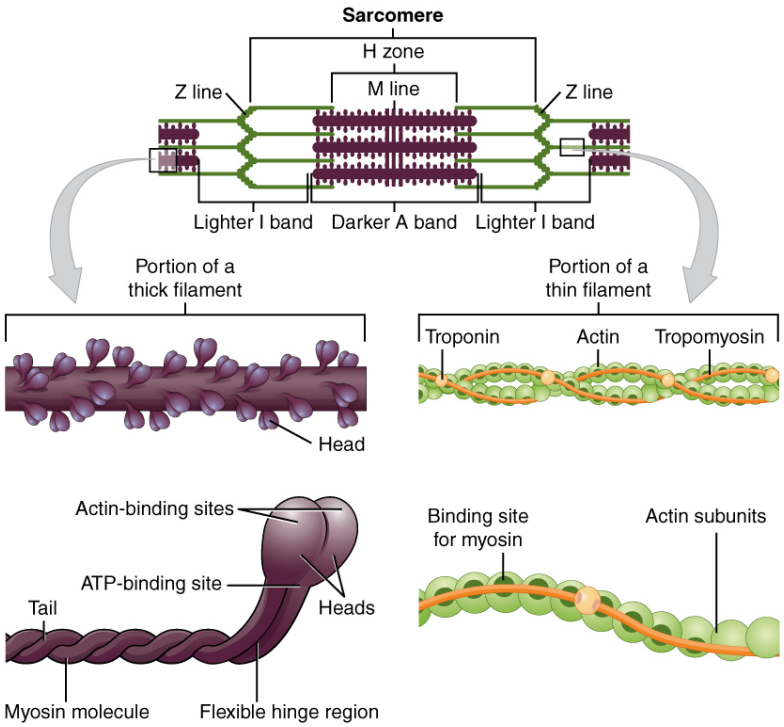


FIGURE 10.5 The Sarcomere The sarcomere, the region from one Z-line to the next Z-line, is the functional unit of a skeletal muscle fiber.

The Neuromuscular Junction

Another specialization of the skeletal muscle is the site where a motor neuron's terminal meets the muscle fiber—called the **neuromuscular junction (NMJ)**. This is where the muscle fiber first responds to signaling by the motor neuron. Every skeletal muscle fiber in every skeletal muscle is innervated by a motor neuron at the NMJ. Excitation signals from the neuron are the only way to functionally activate the fiber to contract.

INTERACTIVE LINK

Every skeletal muscle fiber is supplied by a motor neuron at the NMJ. Watch this video (http://openstax.org/l/skelmuscfiber) to learn more about what happens at the NMJ. (a) What is the definition of a motor unit? (b) What is the structural and functional difference between a large motor unit and a small motor unit? (c) Can you give an example of each? (d) Why is the neurotransmitter acetylcholine degraded after binding to its receptor?

Excitation-Contraction Coupling

All living cells have membrane potentials, or electrical gradients across their membranes. The inside of the membrane is usually around -60 to -90 mV, relative to the outside. This is referred to as a cell's membrane potential. Neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction.

Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

Although the term **excitation-contraction coupling** confuses or scares some students, it comes down to this: for a skeletal muscle fiber to contract, its membrane must first be "excited"—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the sarcolemma as a wave, is "coupled" to the actual contraction through the release of calcium ions (Ca^{++}) from the SR. Once released, the Ca^{++} interacts

Signaling begins when a neuronal **action potential** travels along the axon of a motor neuron, and then along the individual branches to terminate at the NMJ. At the NMJ, the axon terminal releases a chemical messenger, or **neurotransmitter**, called **acetylcholine (ACh)**. The ACh molecules diffuse across a minute space called the **synaptic cleft** and bind to ACh receptors located within the **motor end-plate** of the sarcolemma on the other side of the synapse. Once ACh binds, a channel in the ACh receptor opens and positively charged ions can pass through into the muscle fiber, causing it to **depolarize**, meaning that the membrane potential of the muscle fiber becomes less negative (closer to zero.)

As the membrane depolarizes, another set of ion channels called **voltage-gated sodium channels** are triggered to open. Sodium ions enter the muscle fiber, and an action potential rapidly spreads (or "fires") along the entire membrane to initiate excitation-contraction coupling.

Things happen very quickly in the world of excitable membranes (just think about how quickly you can snap your fingers as soon as you decide to do it). Immediately following depolarization of the membrane, it repolarizes, re-establishing the negative membrane potential. Meanwhile, the ACh in the synaptic cleft is degraded by the enzyme acetylcholinesterase (AChE) so that the ACh cannot rebind to a receptor and reopen its channel, which would cause unwanted extended muscle excitation and contraction.

Propagation of an action potential along the sarcolemma is the excitation portion of excitation-contraction coupling. Recall that this excitation actually triggers the release of calcium ions (Ca^{++}) from its storage in the cell's SR. For the action potential to reach the membrane of the SR, there are periodic invaginations in the sarcolemma, called **T-tubules** ("T" stands for "transverse"). You will recall that the diameter of a muscle fiber can be up to 100 μm, so these T-tubules ensure that the membrane can get close to the SR in the sarcoplasm. The arrangement of a T-tubule with the membranes of SR on either side is called a **triad** (Figure 10.7). The triad surrounds the cylindrical structure called a **myofibril**, which contains actin and myosin.

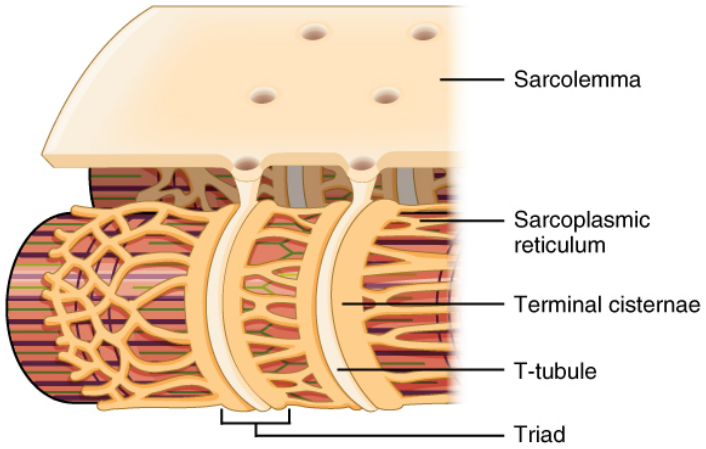


FIGURE 10.7 The T-tubule Narrow T-tubules permit the conduction of electrical impulses. The SR functions to regulate intracellular levels of calcium. Two terminal cisternae (where enlarged SR connects to the T-tubule) and one T-tubule comprise a triad—a "threesome" of membranes, with those of SR on two sides and the T-tubule sandwiched between them.

The T-tubules carry the action potential into the interior of the cell, which triggers the opening of calcium channels in the membrane of the adjacent SR, causing Ca^{++} to diffuse out of the SR and into the sarcoplasm. It is the arrival of Ca^{++} in the sarcoplasm that initiates contraction of the muscle fiber by its contractile units, or sarcomeres.

10.3 Muscle Fiber Contraction and Relaxation

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the components involved in a muscle contraction
- Explain how muscles contract and relax
- Describe the sliding filament model of muscle contraction

The sequence of events that result in the contraction of an individual muscle fiber begins with a signal—the neurotransmitter, ACh—from the motor neuron innervating that fiber. The local membrane of the fiber will depolarize

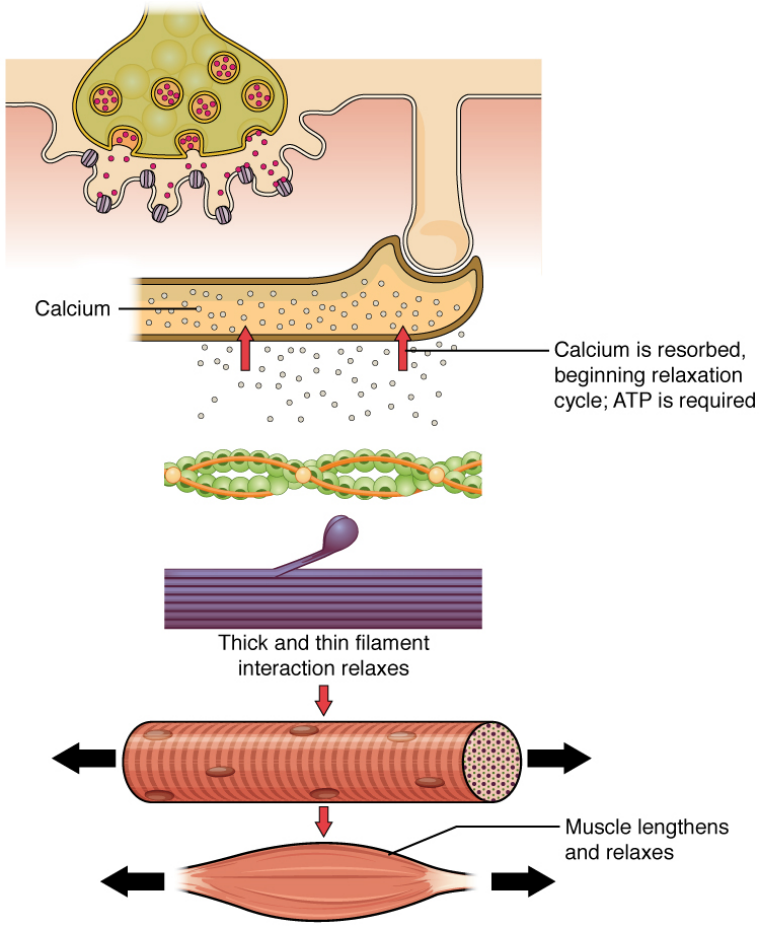


FIGURE 10.9 Relaxation of a Muscle Fiber Ca^{++} ions are pumped back into the SR, which causes the tropomyosin to reshield the binding sites on the actin strands. A muscle may also stop contracting when it runs out of ATP and becomes fatigued.

INTERACTIVE LINK

The release of calcium ions initiates muscle contractions. Watch this video (http://openstax.org/l/calciumrole) to learn more about the role of calcium. (a) What are "T-tubules" and what is their role? (b) Please describe how actin-binding sites are made available for cross-bridging with myosin heads during contraction.

The molecular events of muscle fiber shortening occur within the fiber's sarcomeres (see Figure 10.10). The contraction of a striated muscle fiber occurs as the sarcomeres, linearly arranged within myofibrils, shorten as myosin heads pull on the actin filaments.

The region where thick and thin filaments overlap has a dense appearance, as there is little space between the filaments. This zone where thin and thick filaments overlap is very important to muscle contraction, as it is the site where filament movement starts. Thin filaments, anchored at their ends by the Z-discs, do not extend completely into the central region that only contains thick filaments, anchored at their bases at a spot called the M-line. A myofibril is composed of many sarcomeres running along its length; thus, myofibrils and muscle cells contract as the sarcomeres contract.

The Sliding Filament Model of Contraction

When signaled by a motor neuron, a skeletal muscle fiber contracts as the thin filaments are pulled and then slide past the thick filaments within the fiber's sarcomeres. This process is known as the sliding filament model of muscle contraction (Figure 10.10). The sliding can only occur when myosin-binding sites on the actin filaments are exposed by a series of steps that begins with Ca^{++} entry into the sarcoplasm.

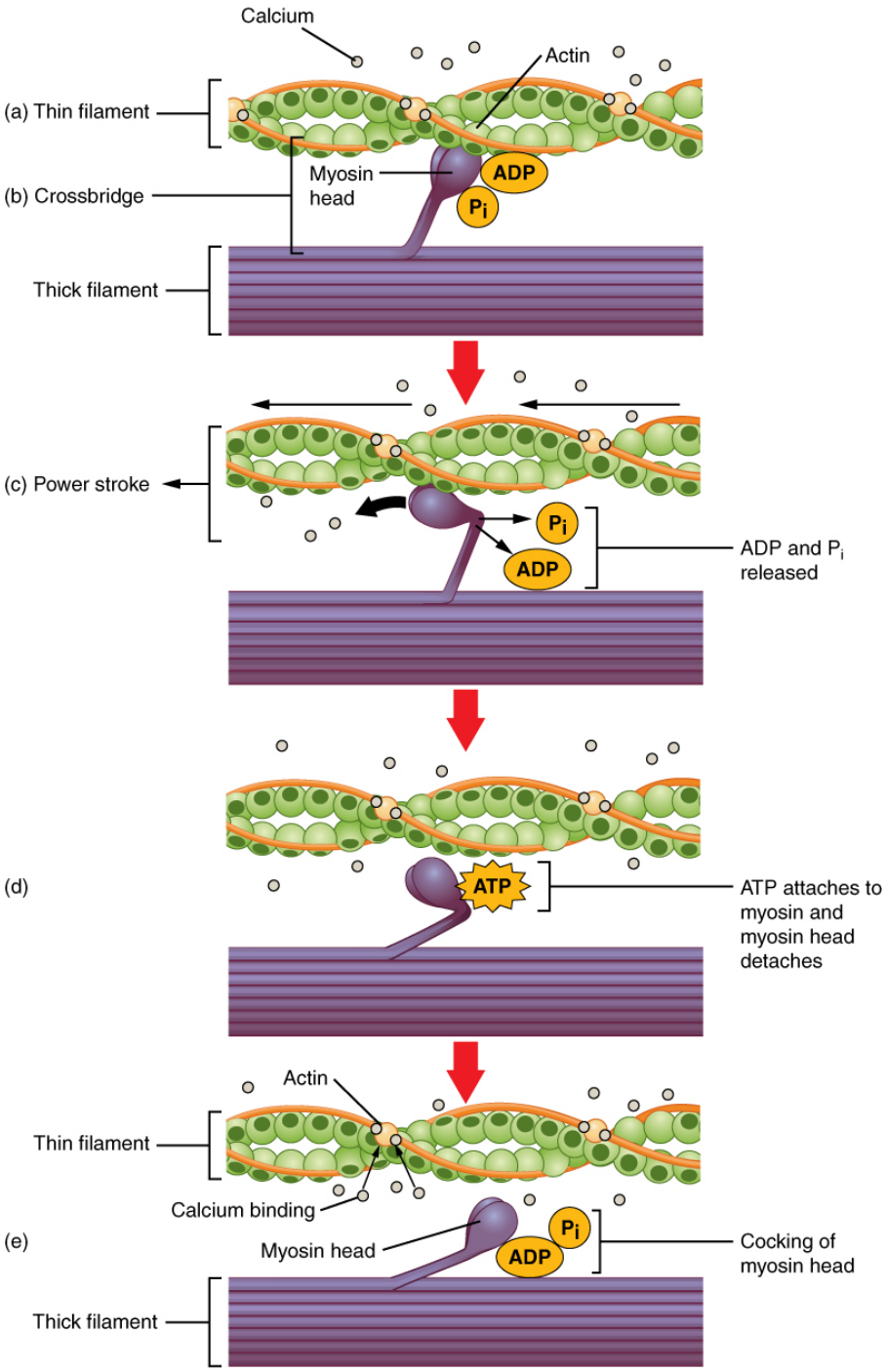
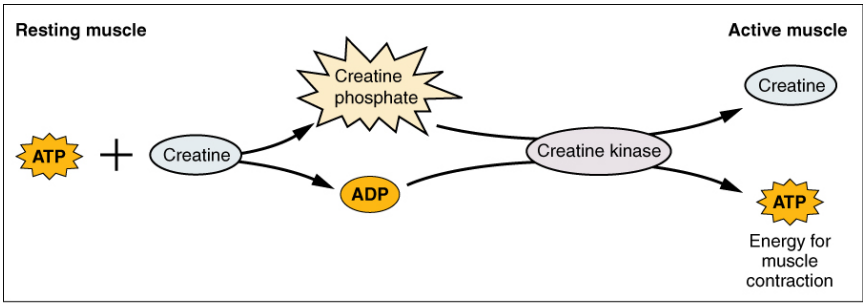


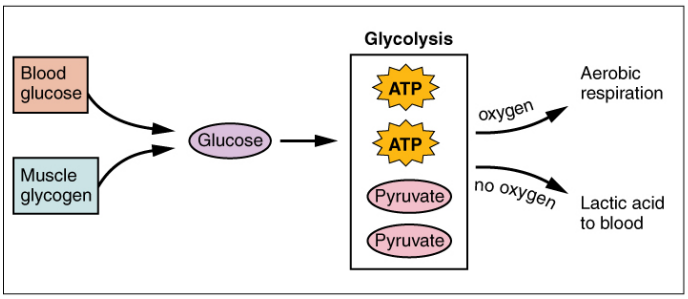
FIGURE 10.11 Skeletal Muscle Contraction (a) The active site on actin is exposed as calcium binds to troponin. (b) The myosin head is attracted to actin, and myosin binds actin at its actin-binding site, forming the cross-bridge. (c) During the power stroke, the phosphate generated in the previous contraction cycle is released. This results in the myosin head pivoting toward the center of the sarcomere, after which the attached ADP and phosphate group are released. (d) A new molecule of ATP attaches to the myosin head, causing the cross-bridge to detach. (e) The myosin head hydrolyzes ATP to ADP and phosphate, which returns the myosin to the cocked position.

Cross-bridge formation occurs when the myosin head attaches to the actin while adenosine diphosphate (ADP) and inorganic phosphate (P_i) are still bound to myosin (Figure 10.11**a,b**). P_i is then released, causing myosin to form a stronger attachment to the actin, after which the myosin head moves toward the M-line, pulling the actin along with it. As actin is pulled, the filaments move approximately 10 nm toward the M-line. This movement is called the **power stroke**, as movement of the thin filament occurs at this step (Figure 10.11**c**). In the absence of ATP, the myosin head will not detach from actin.

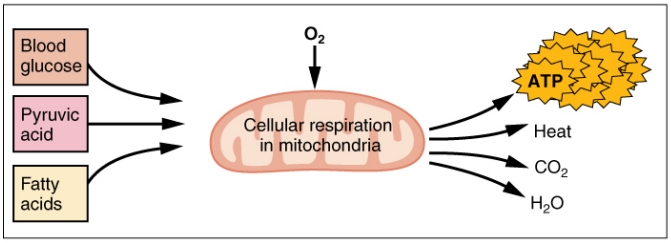
One part of the myosin head attaches to the binding site on the actin, but the head has another binding site for ATP.



(a)



(b)



(c)

FIGURE 10.12 Muscle Metabolism (a) Some ATP is stored in a resting muscle. As contraction starts, it is used up in seconds. More ATP is generated from creatine phosphate for about 15 seconds. (b) Each glucose molecule produces two ATP and two molecules of pyruvic acid, which can be used in aerobic respiration or converted to lactic acid. If oxygen is not available, pyruvic acid is converted to lactic acid, which may contribute to muscle fatigue. This occurs during strenuous exercise when high amounts of energy are needed but oxygen cannot be sufficiently delivered to muscle. (c) Aerobic respiration is the breakdown of glucose in the presence of oxygen (O_2) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria.

As the ATP produced by creatine phosphate is depleted, muscles turn to glycolysis as an ATP source. **Glycolysis** is an anaerobic (non-oxygen-dependent) process that breaks down glucose (sugar) to produce ATP; however, glycolysis cannot generate ATP as quickly as creatine phosphate. Thus, the switch to glycolysis results in a slower rate of ATP availability to the muscle. The sugar used in glycolysis can be provided by blood glucose or by metabolizing glycogen that is stored in the muscle. The breakdown of one glucose molecule produces two ATP and two molecules of **pyruvic acid**, which can be used in aerobic respiration or when oxygen levels are low, converted to lactic acid (Figure 10.12**b**).

If oxygen is available, pyruvic acid is used in aerobic respiration. However, if oxygen is not available, pyruvic acid is converted to **lactic acid**, which may contribute to muscle fatigue. This conversion allows the recycling of the enzyme NAD^+ from NADH, which is needed for glycolysis to continue. This occurs during strenuous exercise when high amounts of energy are needed but oxygen cannot be sufficiently delivered to muscle. Glycolysis itself cannot be sustained for very long (approximately 1 minute of muscle activity), but it is useful in facilitating short bursts of high-intensity output. This is because glycolysis does not utilize glucose very efficiently, producing a net gain of two ATPs per molecule of glucose, and the end product of lactic acid, which may contribute to muscle fatigue as it accumulates.

Aerobic respiration is the breakdown of glucose or other nutrients in the presence of oxygen (O_2) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria. The inputs for aerobic respiration include

Because DMD is caused by a mutation in the gene that codes for dystrophin, it was thought that introducing healthy myoblasts into patients might be an effective treatment. Myoblasts are the embryonic cells responsible for muscle development, and ideally, they would carry healthy genes that could produce the dystrophin needed for normal muscle contraction. This approach has been largely unsuccessful in humans. A recent approach has involved attempting to boost the muscle's production of utrophin, a protein similar to dystrophin that may be able to assume the role of dystrophin and prevent cellular damage from occurring.

10.4 Nervous System Control of Muscle Tension

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain concentric, isotonic, and eccentric contractions
- Describe the length-tension relationship
- Describe the three phases of a muscle twitch
- Define wave summation, tetanus, and treppe

To move an object, referred to as load, the sarcomeres in the muscle fibers of the skeletal muscle must shorten. The force generated by the contraction of the muscle (or shortening of the sarcomeres) is called **muscle tension**. However, muscle tension also is generated when the muscle is contracting against a load that does not move, resulting in two main types of skeletal muscle contractions: isotonic contractions and isometric contractions.

In **isotonic contractions**, where the tension in the muscle stays constant, a load is moved as the length of the muscle changes (shortens). There are two types of isotonic contractions: concentric and eccentric. A **concentric contraction** involves the muscle shortening to move a load. An example of this is the biceps brachii muscle contracting when a hand weight is brought upward with increasing muscle tension. As the biceps brachii contract, the angle of the elbow joint decreases as the forearm is brought toward the body. Here, the biceps brachii contracts as sarcomeres in its muscle fibers are shortening and cross-bridges form; the myosin heads pull the actin. An **eccentric contraction** occurs as the muscle tension diminishes and the muscle lengthens. In this case, the hand weight is lowered in a slow and controlled manner as the amount of cross-bridges being activated by nervous system stimulation decreases. In this case, as tension is released from the biceps brachii, the angle of the elbow joint increases. Eccentric contractions are also used for movement and balance of the body.

An **isometric contraction** occurs as the muscle produces tension without changing the angle of a skeletal joint. Isometric contractions involve sarcomere shortening and increasing muscle tension, but do not move a load, as the force produced cannot overcome the resistance provided by the load. For example, if one attempts to lift a hand weight that is too heavy, there will be sarcomere activation and shortening to a point, and ever-increasing muscle tension, but no change in the angle of the elbow joint. In everyday living, isometric contractions are active in maintaining posture and maintaining bone and joint stability. However, holding your head in an upright position occurs not because the muscles cannot move the head, but because the goal is to remain stationary and not produce movement. Most actions of the body are the result of a combination of isotonic and isometric contractions working together to produce a wide range of outcomes (Figure 10.13).

A large motor unit is an arrangement where a single motor neuron supplies a large number of muscle fibers in a muscle. Large motor units are concerned with simple, or "gross," movements, such as powerfully extending the knee joint. The best example is the large motor units of the thigh muscles or back muscles, where a single motor neuron will supply thousands of muscle fibers in a muscle, as its axon splits into thousands of branches.

There is a wide range of motor units within many skeletal muscles, which gives the nervous system a wide range of control over the muscle. The small motor units in the muscle will have smaller, lower-threshold motor neurons that are more excitable, firing first to their skeletal muscle fibers, which also tend to be the smallest. Activation of these smaller motor units, results in a relatively small degree of contractile strength (tension) generated in the muscle. As more strength is needed, larger motor units, with bigger, higher-threshold motor neurons are enlisted to activate larger muscle fibers. This increasing activation of motor units produces an increase in muscle contraction known as **recruitment**. As more motor units are recruited, the muscle contraction grows progressively stronger. In some muscles, the largest motor units may generate a contractile force of 50 times more than the smallest motor units in the muscle. This allows a feather to be picked up using the biceps brachii arm muscle with minimal force, and a heavy weight to be lifted by the same muscle by recruiting the largest motor units.

When necessary, the maximal number of motor units in a muscle can be recruited simultaneously, producing the maximum force of contraction for that muscle, but this cannot last for very long because of the energy requirements to sustain the contraction. To prevent complete muscle fatigue, motor units are generally not all simultaneously active, but instead some motor units rest while others are active, which allows for longer muscle contractions. The nervous system uses recruitment as a mechanism to efficiently utilize a skeletal muscle.

The Length-Tension Range of a Sarcomere

When a skeletal muscle fiber contracts, myosin heads attach to actin to form cross-bridges followed by the thin filaments sliding over the thick filaments as the heads pull the actin, and this results in sarcomere shortening, creating the tension of the muscle contraction. The cross-bridges can only form where thin and thick filaments already overlap, so that the length of the sarcomere has a direct influence on the force generated when the sarcomere shortens. This is called the length-tension relationship.

The ideal length of a sarcomere to produce maximal tension occurs at 80 percent to 120 percent of its resting length, with 100 percent being the state where the medial edges of the thin filaments are just at the most-medial myosin heads of the thick filaments (Figure 10.14). This length maximizes the overlap of actin-binding sites and myosin heads. If a sarcomere is stretched past this ideal length (beyond 120 percent), thick and thin filaments do not overlap sufficiently, which results in less tension produced. If a sarcomere is shortened beyond 80 percent, the zone of overlap is reduced with the thin filaments jutting beyond the last of the myosin heads and shrinks the H zone, which is normally composed of myosin tails. Eventually, there is nowhere else for the thin filaments to go and the amount of tension is diminished. If the muscle is stretched to the point where thick and thin filaments do not overlap at all, no cross-bridges can be formed, and no tension is produced in that sarcomere. This amount of stretching does not usually occur, as accessory proteins and connective tissue oppose extreme stretching.

Although a person can experience a muscle "twitch," a single twitch does not produce any significant muscle activity in a living body. A series of action potentials to the muscle fibers is necessary to produce a muscle contraction that can produce work. Normal muscle contraction is more sustained, and it can be modified by input from the nervous system to produce varying amounts of force; this is called a **graded muscle response**. The frequency of action potentials (nerve impulses) from a motor neuron and the number of motor neurons transmitting action potentials both affect the tension produced in skeletal muscle.

The rate at which a motor neuron fires action potentials affects the tension produced in the skeletal muscle. If the fibers are stimulated while a previous twitch is still occurring, the second twitch will be stronger. This response is called **wave summation**, because the excitation-contraction coupling effects of successive motor neuron signaling is summed, or added together (Figure 10.16**a**). At the molecular level, summation occurs because the second stimulus triggers the release of more Ca^{++} ions, which become available to activate additional sarcomeres while the muscle is still contracting from the first stimulus. Summation results in greater contraction of the motor unit.

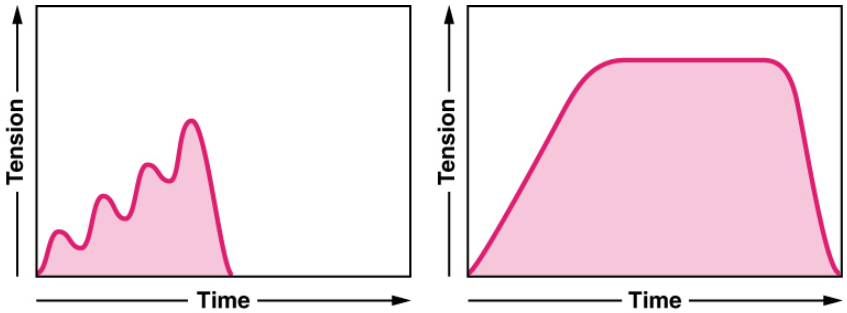


FIGURE 10.16 Wave Summation and Tetanus (a) The excitation-contraction coupling effects of successive motor neuron signaling is added together which is referred to as wave summation. The bottom of each wave, the end of the relaxation phase, represents the point of stimulus. (b) When the stimulus frequency is so high that the relaxation phase disappears completely, the contractions become continuous; this is called tetanus.

If the frequency of motor neuron signaling increases, summation and subsequent muscle tension in the motor unit continues to rise until it reaches a peak point. The tension at this point is about three to four times greater than the tension of a single twitch, a state referred to as incomplete tetanus. During incomplete tetanus, the muscle goes through quick cycles of contraction with a short relaxation phase for each. If the stimulus frequency is so high that the relaxation phase disappears completely, contractions become continuous in a process called complete **tetanus** (Figure 10.16**b**).

During tetanus, the concentration of Ca^{++} ions in the sarcoplasm allows virtually all of the sarcomeres to form cross-bridges and shorten, so that a contraction can continue uninterrupted (until the muscle fatigues and can no longer produce tension).

Treppe

When a skeletal muscle has been dormant for an extended period and then activated to contract, with all other things being equal, the initial contractions generate about one-half the force of later contractions. The muscle tension increases in a graded manner that to some looks like a set of stairs. This tension increase is called **treppe**, a condition where muscle contractions become more efficient. It's also known as the "staircase effect" (Figure 10.17).

metabolic cycle, making the fiber more resistant to fatigue. Glycolytic fibers primarily create ATP through anaerobic glycolysis, which produces less ATP per cycle. As a result, glycolytic fibers fatigue at a quicker rate.

The oxidative fibers contain many more mitochondria than the glycolytic fibers, because aerobic metabolism, which uses oxygen (O_2) in the metabolic pathway, occurs in the mitochondria. The SO fibers possess a large number of mitochondria and are capable of contracting for longer periods because of the large amount of ATP they can produce, but they have a relatively small diameter and do not produce a large amount of tension. SO fibers are extensively supplied with blood capillaries to supply O_2 from the red blood cells in the bloodstream. The SO fibers also possess myoglobin, an O_2-carrying molecule similar to O_2-carrying hemoglobin in the red blood cells. The myoglobin stores some of the needed O_2 within the fibers themselves (and gives SO fibers their red color). All of these features allow SO fibers to produce large quantities of ATP, which can sustain muscle activity without fatiguing for long periods of time.

The fact that SO fibers can function for long periods without fatiguing makes them useful in maintaining posture, producing isometric contractions, stabilizing bones and joints, and making small movements that happen often but do not require large amounts of energy. They do not produce high tension, and thus they are not used for powerful, fast movements that require high amounts of energy and rapid cross-bridge cycling.

FO fibers are sometimes called intermediate fibers because they possess characteristics that are intermediate between fast fibers and slow fibers. They produce ATP relatively quickly, more quickly than SO fibers, and thus can produce relatively high amounts of tension. They are oxidative because they produce ATP aerobically, possess high amounts of mitochondria, and do not fatigue quickly. However, FO fibers do not possess significant myoglobin, giving them a lighter color than the red SO fibers. FO fibers are used primarily for movements, such as walking, that require more energy than postural control but less energy than an explosive movement, such as sprinting. FO fibers are useful for this type of movement because they produce more tension than SO fibers but they are more fatigue-resistant than FG fibers.

FG fibers primarily use anaerobic glycolysis as their ATP source. They have a large diameter and possess high amounts of glycogen, which is used in glycolysis to generate ATP quickly to produce high levels of tension. Because they do not primarily use aerobic metabolism, they do not possess substantial numbers of mitochondria or significant amounts of myoglobin and therefore have a white color. FG fibers are used to produce rapid, forceful contractions to make quick, powerful movements. These fibers fatigue quickly, permitting them to only be used for short periods. Most muscles possess a mixture of each fiber type. The predominant fiber type in a muscle is determined by the primary function of the muscle.

10.6 Exercise and Muscle Performance

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe hypertrophy and atrophy
- Explain how resistance exercise builds muscle
- Explain how performance-enhancing substances affect muscle

Physical training alters the appearance of skeletal muscles and can produce changes in muscle performance. Conversely, a lack of use can result in decreased performance and muscle appearance. Although muscle cells can change in size, new cells are not formed when muscles grow. Instead, structural proteins are added to muscle fibers in a process called **hypertrophy**, so cell diameter increases. The reverse, when structural proteins are lost and muscle mass decreases, is called **atrophy**. Age-related muscle atrophy is called **sarcopenia**. Cellular components of muscles can also undergo changes in response to changes in muscle use.

Endurance Exercise

Slow fibers are predominantly used in endurance exercises that require little force but involve numerous repetitions. The aerobic metabolism used by slow-twitch fibers allows them to maintain contractions over long periods. Endurance training modifies these slow fibers to make them even more efficient by producing more mitochondria to enable more aerobic metabolism and more ATP production. Endurance exercise can also increase the amount of myoglobin in a cell, as increased aerobic respiration increases the need for oxygen. Myoglobin is found in the



FIGURE 10.19 Hypertrophy Body builders have a large number of FG fibers and relatively few FO and SO fibers. (credit: Lin Mei/flickr)

Except for the hypertrophy that follows an increase in the number of sarcomeres and myofibrils in a skeletal muscle, the cellular changes observed during endurance training do not usually occur with resistance training. There is usually no significant increase in mitochondria or capillary density. However, resistance training does increase the development of connective tissue, which adds to the overall mass of the muscle and helps to contain muscles as they produce increasingly powerful contractions. Tendons also become stronger to prevent tendon damage, as the force produced by muscles is transferred to tendons that attach the muscle to bone.

For effective strength training, the intensity of the exercise must continually be increased. For instance, continued weight lifting without increasing the weight of the load does not increase muscle size. To produce ever-greater results, the weights lifted must become increasingly heavier, making it more difficult for muscles to move the load. The muscle then adapts to this heavier load, and an even heavier load must be used if even greater muscle mass is desired.

If done improperly, resistance training can lead to overuse injuries of the muscle, tendon, or bone. These injuries can occur if the load is too heavy or if the muscles are not given sufficient time between workouts to recover or if joints are not aligned properly during the exercises. Cellular damage to muscle fibers that occurs after intense exercise includes damage to the sarcolemma and myofibrils. This muscle damage contributes to the feeling of soreness after strenuous exercise, but muscles gain mass as this damage is repaired, and additional structural proteins are added to replace the damaged ones. Overworking skeletal muscles can also lead to tendon damage and even skeletal damage if the load is too great for the muscles to bear.

Performance-Enhancing Substances

Some athletes attempt to boost their performance by using various agents that may enhance muscle performance. Anabolic steroids are one of the more widely known agents used to boost muscle mass and increase power output. Anabolic steroids are a form of testosterone, a male sex hormone that stimulates muscle formation, leading to increased muscle mass.

Endurance athletes may also try to boost the availability of oxygen to muscles to increase aerobic respiration by using substances such as erythropoietin (EPO), a hormone normally produced in the kidneys, which triggers the production of red blood cells. The extra oxygen carried by these blood cells can then be used by muscles for aerobic respiration. Human growth hormone (hGH) is another supplement, and although it can facilitate building muscle mass, its main role is to promote the healing of muscle and other tissues after strenuous exercise. Increased hGH may allow for faster recovery after muscle damage, reducing the rest required after exercise, and allowing for more sustained high-level performance.

Although performance-enhancing substances often do improve performance, most are banned by governing bodies in sports and are illegal for nonmedical purposes. Their use to enhance performance raises ethical issues of cheating because they give users an unfair advantage over nonusers. A greater concern, however, is that their use carries serious health risks. The side effects of these substances are often significant, nonreversible, and in some cases fatal. The physiological strain caused by these substances is often greater than what the body can handle,

sarcomeres, possessing the same banding organization as skeletal muscle (Figure 10.21). However, cardiac muscle fibers are shorter than skeletal muscle fibers and usually contain only one nucleus, which is located in the central region of the cell. Cardiac muscle fibers also possess many mitochondria and myoglobin, as ATP is produced primarily through aerobic metabolism. Cardiac muscle fibers cells also are extensively branched and are connected to one another at their ends by intercalated discs. An **intercalated disc** allows the cardiac muscle cells to contract in a wave-like pattern so that the heart can work as a pump.

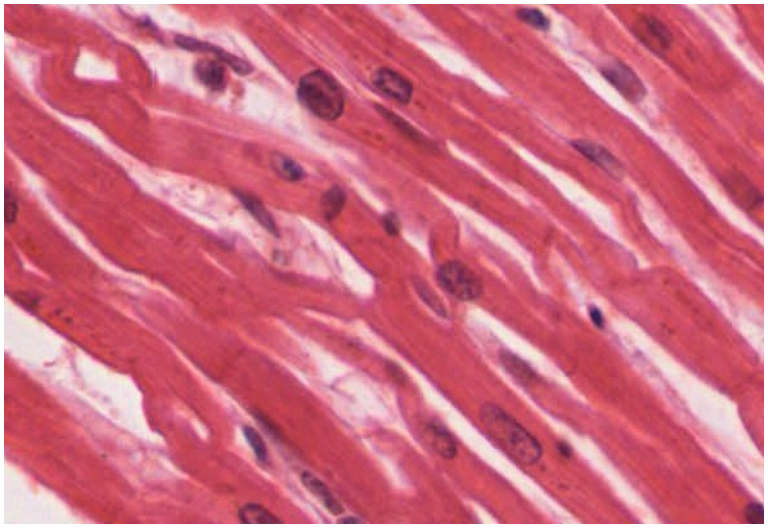


FIGURE 10.21 Cardiac Muscle Tissue Cardiac muscle tissue is only found in the heart. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/cardmuscleMG) to explore the tissue sample in greater detail.

Intercalated discs are part of the sarcolemma and contain two structures important in cardiac muscle contraction: gap junctions and desmosomes. A gap junction forms channels between adjacent cardiac muscle fibers that allow the depolarizing current produced by cations to flow from one cardiac muscle cell to the next. This joining is called electric coupling, and in cardiac muscle it allows the quick transmission of action potentials and the coordinated contraction of the entire heart. This network of electrically connected cardiac muscle cells creates a functional unit of contraction called a syncytium. The remainder of the intercalated disc is composed of desmosomes. A **desmosome** is a cell structure that anchors the ends of cardiac muscle fibers together so the cells do not pull apart during the stress of individual fibers contracting (Figure 10.22).

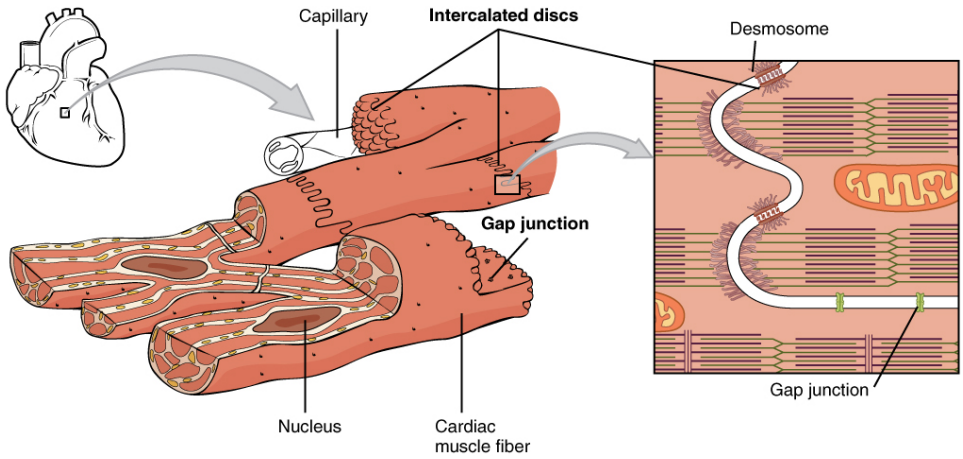


FIGURE 10.22 Cardiac Muscle Intercalated discs are part of the cardiac muscle sarcolemma and they contain gap junctions and desmosomes.

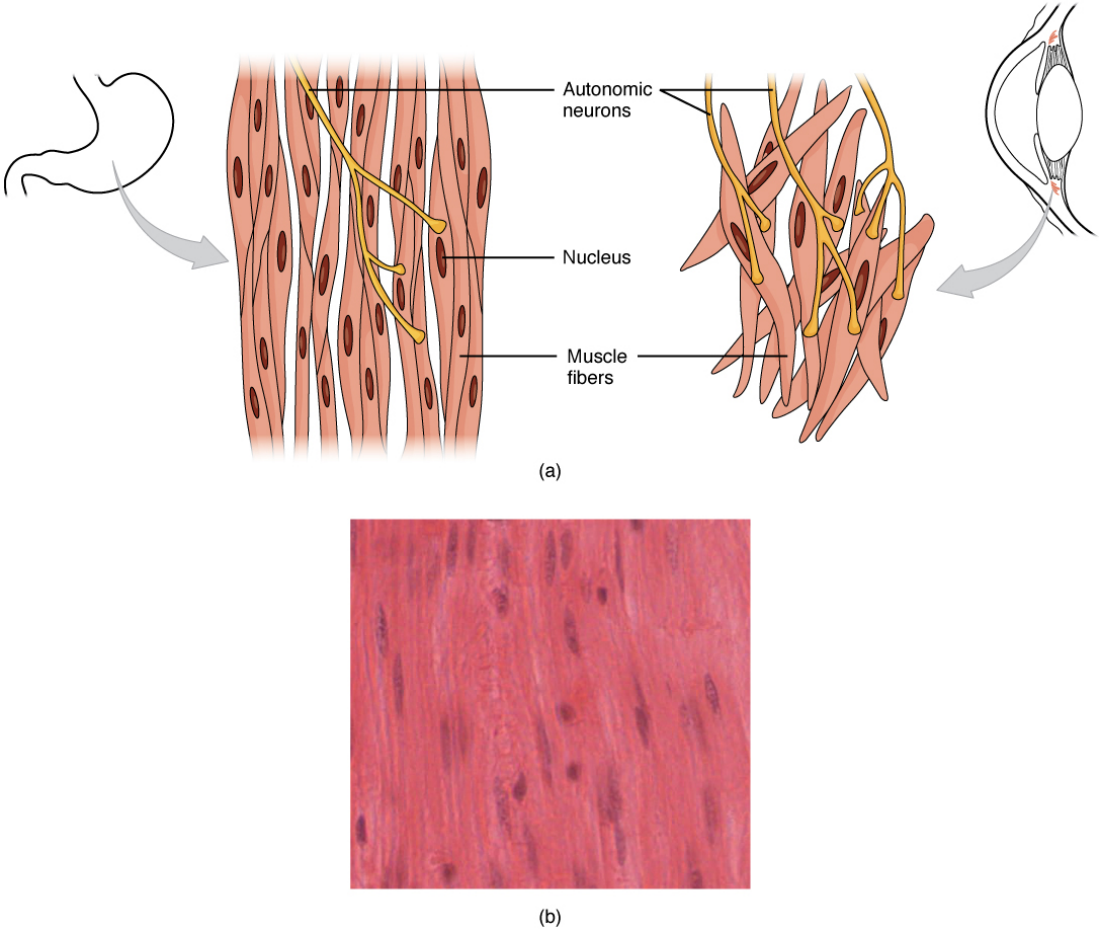


FIGURE 10.23 **Smooth Muscle Tissue** Smooth muscle tissue is found around organs in the digestive, respiratory, reproductive tracts and the iris of the eye. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/smoothmuscMG) to explore the tissue sample in greater detail.

Smooth muscle fibers are spindle-shaped (wide in the middle and tapered at both ends, somewhat like a football) and have a single nucleus; they range from about 30 to 200 μm (thousands of times shorter than skeletal muscle fibers), and they produce their own connective tissue, endomysium. Although they do not have striations and sarcomeres, smooth muscle fibers do have actin and myosin contractile proteins, and thick and thin filaments. These thin filaments are anchored by dense bodies. A **dense body** is analogous to the Z-discs of skeletal and cardiac muscle fibers and is fastened to the sarcolemma. Calcium ions are supplied by the SR in the fibers and by sequestration from the extracellular fluid through membrane indentations called calveoli.

Because smooth muscle cells do not contain troponin, cross-bridge formation is not regulated by the troponin-tropomyosin complex but instead by the regulatory protein **calmodulin**. In a smooth muscle fiber, external Ca^{++} ions passing through opened calcium channels in the sarcolemma, and additional Ca^{++} released from SR, bind to calmodulin. The Ca^{++}-calmodulin complex then activates an enzyme called myosin (light chain) kinase, which, in turn, activates the myosin heads by phosphorylating them (converting ATP to ADP and P_i, with the P_i attaching to the head). The heads can then attach to actin-binding sites and pull on the thin filaments. The thin filaments also are anchored to the dense bodies; the structures invested in the inner membrane of the sarcolemma (at adherens junctions) that also have cord-like intermediate filaments attached to them. When the thin filaments slide past the thick filaments, they pull on the dense bodies, structures tethered to the sarcolemma, which then pull on the intermediate filaments networks throughout the sarcoplasm. This arrangement causes the entire muscle fiber to contract in a manner whereby the ends are pulled toward the center, causing the midsection to bulge in a corkscrew

Smooth muscle is organized in two ways: as single-unit smooth muscle, which is much more common; and as multiunit smooth muscle. The two types have different locations in the body and have different characteristics. Single-unit muscle has its muscle fibers joined by gap junctions so that the muscle contracts as a single unit. This type of smooth muscle is found in the walls of all visceral organs except the heart (which has cardiac muscle in its walls), and so it is commonly called **visceral muscle**. Because the muscle fibers are not constrained by the organization and stretchability limits of sarcomeres, visceral smooth muscle has a **stress-relaxation response**. This means that as the muscle of a hollow organ is stretched when it fills, the mechanical stress of the stretching will trigger contraction, but this is immediately followed by relaxation so that the organ does not empty its contents prematurely. This is important for hollow organs, such as the stomach or urinary bladder, which continuously expand as they fill. The smooth muscle around these organs also can maintain a muscle tone when the organ empties and shrinks, a feature that prevents "flabbiness" in the empty organ. In general, visceral smooth muscle produces slow, steady contractions that allow substances, such as food in the digestive tract, to move through the body.

Multiunit smooth muscle cells rarely possess gap junctions, and thus are not electrically coupled. As a result, contraction does not spread from one cell to the next, but is instead confined to the cell that was originally stimulated. Stimuli for multiunit smooth muscles come from autonomic nerves or hormones but not from stretching. This type of tissue is found around large blood vessels, in the respiratory airways, and in the eyes.

Hyperplasia in Smooth Muscle

Similar to skeletal and cardiac muscle cells, smooth muscle can undergo hypertrophy to increase in size. Unlike other muscle, smooth muscle can also divide to produce more cells, a process called **hyperplasia**. This can most evidently be observed in the uterus at puberty, which responds to increased estrogen levels by producing more uterine smooth muscle fibers, and greatly increases the size of the myometrium.

10.9 Development and Regeneration of Muscle Tissue

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the function of satellite cells
- Define fibrosis
- Explain which muscle has the greatest regeneration ability

Most muscle tissue of the body arises from embryonic mesoderm. Paraxial mesodermal cells adjacent to the neural tube form blocks of cells called **somites**. Skeletal muscles, excluding those of the head and limbs, develop from mesodermal somites, whereas skeletal muscle in the head and limbs develop from general mesoderm. Somites give rise to myoblasts. A **myoblast** is a muscle-forming stem cell that migrates to different regions in the body and then fuse(s) to form a syncytium, or **myotube**. As a myotube is formed from many different myoblast cells, it contains many nuclei, but has a continuous cytoplasm. This is why skeletal muscle cells are multinucleate, as the nucleus of each contributing myoblast remains intact in the mature skeletal muscle cell. However, cardiac and smooth muscle cells are not multinucleate because the myoblasts that form their cells do not fuse.

Gap junctions develop in the cardiac and single-unit smooth muscle in the early stages of development. In skeletal muscles, ACh receptors are initially present along most of the surface of the myoblasts, but spinal nerve innervation causes the release of growth factors that stimulate the formation of motor end-plates and NMJs. As neurons become active, electrical signals that are sent through the muscle influence the distribution of slow and fast fibers in the muscle.

Although the number of muscle cells is set during development, satellite cells help to repair skeletal muscle cells. A **satellite cell** is similar to a myoblast because it is a type of stem cell; however, satellite cells are incorporated into muscle cells and facilitate the protein synthesis required for repair and growth. These cells are located outside the sarcolemma and are stimulated to grow and fuse with muscle cells by growth factors that are released by muscle fibers under certain forms of stress. Satellite cells can regenerate muscle fibers to a very limited extent, but they primarily help to repair damage in living cells. If a cell is damaged to a greater extent than can be repaired by satellite cells, the muscle fibers are replaced by scar tissue in a process called **fibrosis**. Because scar tissue cannot contract, muscle that has sustained significant damage loses strength and cannot produce the same amount of power or endurance as it could before being damaged.

Key Terms

acetylcholine (ACh) neurotransmitter that binds at a motor end-plate to trigger depolarization
actin protein that makes up most of the thin myofilaments in a sarcomere muscle fiber
action potential change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers
aerobic respiration production of ATP in the presence of oxygen
angiogenesis formation of blood capillary networks
aponeurosis broad, tendon-like sheet of connective tissue that attaches a skeletal muscle to another skeletal muscle or to a bone
ATPase enzyme that hydrolyzes ATP to ADP
atrophy loss of structural proteins from muscle fibers
autorhythmicity heart's ability to control its own contractions
calmodulin regulatory protein that facilitates contraction in smooth muscles
cardiac muscle striated muscle found in the heart; joined to one another at intercalated discs and under the regulation of pacemaker cells, which contract as one unit to pump blood through the circulatory system. Cardiac muscle is under involuntary control.
concentric contraction muscle contraction that shortens the muscle to move a load
contractility ability to shorten (contract) forcibly
contraction phase twitch contraction phase when tension increases
creatine phosphate phosphagen used to store energy from ATP and transfer it to muscle
dense body sarcoplasmic structure that attaches to the sarcolemma and shortens the muscle as thin filaments slide past thick filaments
depolarize to reduce the voltage difference between the inside and outside of a cell's plasma membrane (the sarcolemma for a muscle fiber), making the inside less negative than at rest
desmosome cell structure that anchors the ends of cardiac muscle fibers to allow contraction to occur
eccentric contraction muscle contraction that lengthens the muscle as the tension is diminished
elasticity ability to stretch and rebound
endomysium loose, and well-hydrated connective tissue covering each muscle fiber in a skeletal muscle
epimysium outer layer of connective tissue around a skeletal muscle
excitability ability to undergo neural stimulation
excitation-contraction coupling sequence of events from motor neuron signaling to a skeletal muscle fiber to contraction of the fiber's sarcomeres
extensibility ability to lengthen (extend)
fascicle bundle of muscle fibers within a skeletal muscle
fast glycolytic (FG) muscle fiber that primarily uses anaerobic glycolysis
fast oxidative (FO) intermediate muscle fiber that is between slow oxidative and fast glycolytic fibers
fibrosis replacement of muscle fibers by scar tissue
glycolysis anaerobic breakdown of glucose to ATP
graded muscle response modification of contraction strength
hyperplasia process in which one cell splits to produce new cells
hypertonia abnormally high muscle tone
hypertrophy addition of structural proteins to muscle fibers
hypotonia abnormally low muscle tone caused by the absence of low-level contractions
intercalated disc part of the sarcolemma that connects cardiac tissue, and contains gap junctions and desmosomes
isometric contraction muscle contraction that occurs with no change in muscle length
isotonic contraction muscle contraction that involves changes in muscle length
lactic acid product of anaerobic glycolysis
latch-bridges subset of a cross-bridge in which actin and myosin remain locked together
latent period the time when a twitch does not produce contraction
motor end-plate sarcolemma of muscle fiber at the neuromuscular junction, with receptors for the neurotransmitter acetylcholine
motor unit motor neuron and the group of muscle fibers it innervates
muscle tension force generated by the contraction of the muscle; tension generated during isotonic contractions and isometric contractions
muscle tone low levels of muscle contraction that occur when a muscle is not producing movement
myoblast muscle-forming stem cell
myofibril long, cylindrical organelle that runs parallel within the muscle fiber and contains the sarcomeres
myogram instrument used to measure twitch tension
myosin protein that makes up most of the thick cylindrical myofilament within a sarcomere muscle fiber
myotube fusion of many myoblast cells
neuromuscular junction (NMJ) synapse between the axon terminal of a motor neuron and the section of

attach to bones directly or through tendons or aponeuroses. Skeletal muscles maintain posture, stabilize bones and joints, control internal movement, and generate heat.

Skeletal muscle fibers are long, multinucleated cells. The membrane of the cell is the sarcolemma; the cytoplasm of the cell is the sarcoplasm. The sarcoplasmic reticulum (SR) is a form of endoplasmic reticulum. Muscle fibers are composed of myofibrils. The striations are created by the organization of actin and myosin resulting in the banding pattern of myofibrils.

10.3 Muscle Fiber Contraction and Relaxation

A sarcomere is the smallest contractile portion of a muscle. Myofibrils are composed of thick and thin filaments. Thick filaments are composed of the protein myosin; thin filaments are composed of the protein actin. Troponin and tropomyosin are regulatory proteins.

Muscle contraction is described by the sliding filament model of contraction. ACh is the neurotransmitter that binds at the neuromuscular junction (NMJ) to trigger depolarization, and an action potential travels along the sarcolemma to trigger calcium release from SR. The actin sites are exposed after Ca^{++} enters the sarcoplasm from its SR storage to activate the troponin-tropomyosin complex so that the tropomyosin shifts away from the sites. The cross-bridging of myosin heads docking into actin-binding sites is followed by the "power stroke"—the sliding of the thin filaments by thick filaments. The power strokes are powered by ATP. Ultimately, the sarcomeres, myofibrils, and muscle fibers shorten to produce movement.

10.4 Nervous System Control of Muscle Tension

The number of cross-bridges formed between actin and myosin determines the amount of tension produced by a muscle. The length of a sarcomere is optimal when the zone of overlap between thin and thick filaments is greatest. Muscles that are stretched or compressed too greatly do not produce maximal amounts of power. A motor unit is formed by a motor neuron and all of the muscle fibers that are innervated by that same motor neuron. A single contraction is called a twitch. A muscle twitch has a latent period, a contraction phase, and a relaxation phase. A graded muscle response allows variation in muscle tension. Summation occurs as successive stimuli are added together to produce a stronger muscle contraction. Tetanus is the fusion of contractions to produce a continuous contraction. Increasing the number of motor neurons involved increases the amount of motor units activated in a muscle, which is called recruitment. Muscle tone is the constant low-level contractions that allow for posture and stability.

10.5 Types of Muscle Fibers

ATP provides the energy for muscle contraction. The three mechanisms for ATP regeneration are creatine phosphate, anaerobic glycolysis, and aerobic metabolism. Creatine phosphate provides about the first 15 seconds of ATP at the beginning of muscle contraction. Anaerobic glycolysis produces small amounts of ATP in the absence of oxygen for a short period. Aerobic metabolism utilizes oxygen to produce much more ATP, allowing a muscle to work for longer periods. Muscle fatigue, which has many contributing factors, occurs when muscle can no longer contract. An oxygen debt is created as a result of muscle use. The three types of muscle fiber are slow oxidative (SO), fast oxidative (FO) and fast glycolytic (FG). SO fibers use aerobic metabolism to produce low power contractions over long periods and are slow to fatigue. FO fibers use aerobic metabolism to produce ATP but produce higher tension contractions than SO fibers. FG fibers use anaerobic metabolism to produce powerful, high-tension contractions but fatigue quickly.

10.6 Exercise and Muscle Performance

Hypertrophy is an increase in muscle mass due to the addition of structural proteins. The opposite of hypertrophy is atrophy, the loss of muscle mass due to the breakdown of structural proteins. Endurance exercise causes an increase in cellular mitochondria, myoglobin, and capillary networks in SO fibers. Endurance athletes have a high level of SO fibers relative to the other fiber types. Resistance exercise causes hypertrophy. Power-producing muscles have a higher number of FG fibers than of slow fibers. Strenuous exercise causes muscle cell damage that requires time to heal. Some athletes use performance-enhancing substances to enhance muscle performance. Muscle atrophy due to age is called sarcopenia and occurs as muscle fibers die and are replaced by connective and adipose tissue.

10.7 Cardiac Muscle Tissue

Cardiac muscle is striated muscle that is present only in the heart. Cardiac muscle fibers have a single nucleus, are branched, and joined to one another by intercalated discs that contain gap junctions for

Review Questions

4. Muscle that has a striped appearance is described as being _____.
   a. elastic
   b. nonstriated
   c. excitable
   d. striated

5. Which element is important in directly triggering contraction?
   a. sodium (Na^+)
   b. calcium (Ca^{++})
   c. potassium (K^+)
   d. chloride (Cl^-)

6. Which of the following properties is *not* common to all three muscle tissues?
   a. excitability
   b. the need for ATP
   c. at rest, uses shielding proteins to cover actin-binding sites
   d. elasticity

7. The correct order for the smallest to the largest unit of organization in muscle tissue is _____.
   a. fascicle, filament, muscle fiber, myofibril
   b. filament, myofibril, muscle fiber, fascicle
   c. muscle fiber, fascicle, filament, myofibril
   d. myofibril, muscle fiber, filament, fascicle

8. Depolarization of the sarcolemma means _____.
   a. the inside of the membrane has become less negative as sodium ions accumulate
   b. the outside of the membrane has become less negative as sodium ions accumulate
   c. the inside of the membrane has become more negative as sodium ions accumulate
   d. the sarcolemma has completely lost any electrical charge

9. In relaxed muscle, the myosin-binding site on actin is blocked by _____.
   a. titin
   b. troponin
   c. myoglobin
   d. tropomyosin

10. According to the sliding filament model, binding sites on actin open when _____.
   a. creatine phosphate levels rise
   b. ATP levels rise
   c. acetylcholine levels rise
   d. calcium ion levels rise

11. The cell membrane of a muscle fiber is called _____.
   a. myofibril
   b. sarcolemma
   c. sarcoplasm
   d. myofilament

12. Muscle relaxation occurs when _____.
   a. calcium ions are actively transported out of the sarcoplasmic reticulum
   b. calcium ions diffuse out of the sarcoplasmic reticulum
   c. calcium ions are actively transported into the sarcoplasmic reticulum
   d. calcium ions diffuse into the sarcoplasmic reticulum

13. During muscle contraction, the cross-bridge detaches when _____.
   a. the myosin head binds to an ADP molecule
   b. the myosin head binds to an ATP molecule
   c. calcium ions bind to troponin
   d. calcium ions bind to actin

14. Thin and thick filaments are organized into functional units called _____.
   a. myofibrils
   b. myofilaments
   c. T-tubules
   d. sarcomeres

15. During which phase of a twitch in a muscle fiber is tension the greatest?
   a. resting phase
   b. repolarization phase
   c. contraction phase
   d. relaxation phase

16. Muscle fatigue is caused by _____.
   a. buildup of ATP and lactic acid levels
   b. exhaustion of energy reserves and buildup of lactic acid levels
   c. buildup of ATP and pyruvic acid levels
   d. exhaustion of energy reserves and buildup of pyruvic acid levels

Critical Thinking Questions

30. Why is elasticity an important quality of muscle tissue?
31. What would happen to skeletal muscle if the epimysium were destroyed?
32. Describe how tendons facilitate body movement.
33. What are the five primary functions of skeletal muscle?
34. What are the opposite roles of voltage-gated sodium channels and voltage-gated potassium channels?
35. How would muscle contractions be affected if skeletal muscle fibers did not have T-tubules?
36. What causes the striated appearance of skeletal muscle tissue?
37. How would muscle contractions be affected if ATP was completely depleted in a muscle fiber?
38. Why does a motor unit of the eye have few muscle fibers compared to a motor unit of the leg?
39. What factors contribute to the amount of tension produced in an individual muscle fiber?
40. Why do muscle cells use creatine phosphate instead of glycolysis to supply ATP for the first few seconds of muscle contraction?
41. Is aerobic respiration more or less efficient than glycolysis? Explain your answer.
42. What changes occur at the cellular level in response to endurance training?
43. What changes occur at the cellular level in response to resistance training?
44. What would be the drawback of cardiac contractions being the same duration as skeletal muscle contractions?
45. How are cardiac muscle cells similar to and different from skeletal muscle cells?
46. Why can smooth muscles contract over a wider range of resting lengths than skeletal and cardiac muscle?
47. Describe the differences between single-unit smooth muscle and multiunit smooth muscle.
48. Why is muscle that has sustained significant damage unable to produce the same amount of power as it could before being damaged?
49. Which muscle type(s) (skeletal, smooth, or cardiac) can regenerate new muscle cells/fibers? Explain your answer.

To move the skeleton, the tension created by the contraction of the fibers in most skeletal muscles is transferred to the tendons. The tendons are strong bands of dense, regular connective tissue that connect muscles to bones. The bone connection is why this muscle tissue is called skeletal muscle.

Interactions of Skeletal Muscles in the Body

To pull on a bone, that is, to change the angle at its synovial joint, which essentially moves the skeleton, a skeletal muscle must also be attached to a fixed part of the skeleton. The moveable end of the muscle that attaches to the bone being pulled is called the muscle's **insertion**, and the end of the muscle attached to a fixed (stabilized) bone is called the **origin**. During forearm **flexion**—bending the elbow—the brachioradialis assists the brachialis.

Although a number of muscles may be involved in an action, the principal muscle involved is called the **prime mover**, or **agonist**. To lift a cup, a muscle called the biceps brachii is actually the prime mover; however, because it can be assisted by the brachialis, the brachialis is called a **synergist** in this action (Figure 11.2). A synergist can also be a **fixator** that stabilizes the bone that is the attachment for the prime mover's origin.

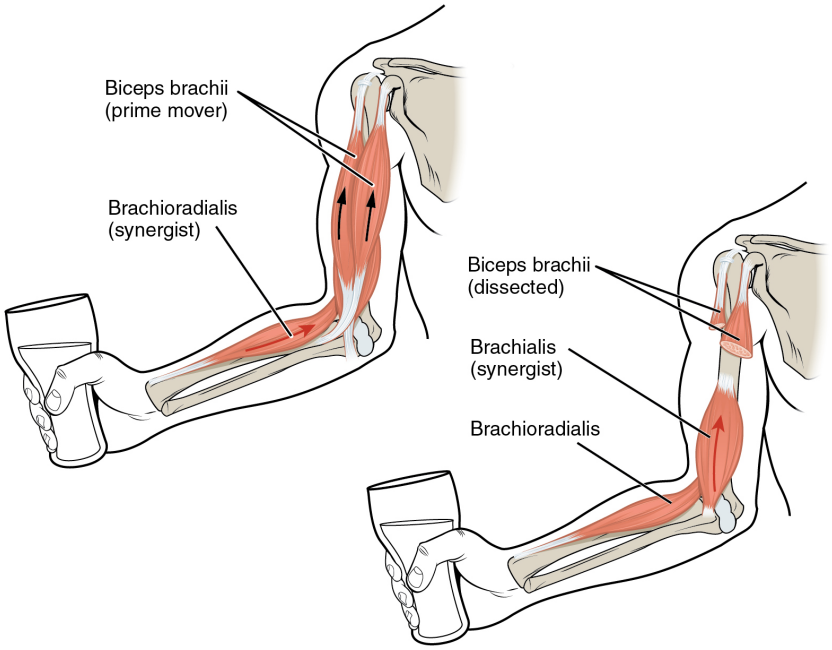


FIGURE 11.2 Prime Movers and Synergists The biceps brachii flex the lower arm. The brachoradialis, in the forearm, and brachialis, located deep to the biceps in the upper arm, are both synergists that aid in this motion.

A muscle with the opposite action of the prime mover is called an **antagonist**. Antagonists play two important roles in muscle function: (1) they maintain body or limb position, such as holding the arm out or standing erect; and (2) they control rapid movement, as in shadow boxing without landing a punch or the ability to check the motion of a limb.

For example, to extend the knee, a group of four muscles called the quadriceps femoris in the anterior compartment of the thigh are activated (and would be called the agonists of knee extension). However, to flex the knee joint, an opposite or antagonistic set of muscles called the hamstrings is activated.

As you can see, these terms would also be reversed for the opposing action. If you consider the first action as the knee bending, the hamstrings would be called the agonists and the quadriceps femoris would then be called the antagonists. See Table 11.1 for a list of some agonists and antagonists.

Parallel muscles have fascicles that are arranged in the same direction as the long axis of the muscle (Figure 11.3). The majority of skeletal muscles in the body have this type of organization. Some parallel muscles are flat sheets that expand at the ends to make broad attachments. Other parallel muscles are rotund with tendons at one or both ends. Muscles that seem to be plump have a large mass of tissue located in the middle of the muscle, between the insertion and the origin, which is known as the central body. A more common name for this muscle is **belly**. When a muscle contracts, the contractile fibers shorten it to an even larger bulge. For example, extend and then flex your biceps brachii muscle; the large, middle section is the belly (Figure 11.4). When a parallel muscle has a central, large belly that is spindle-shaped, meaning it tapers as it extends to its origin and insertion, it sometimes is called **fusiform**.

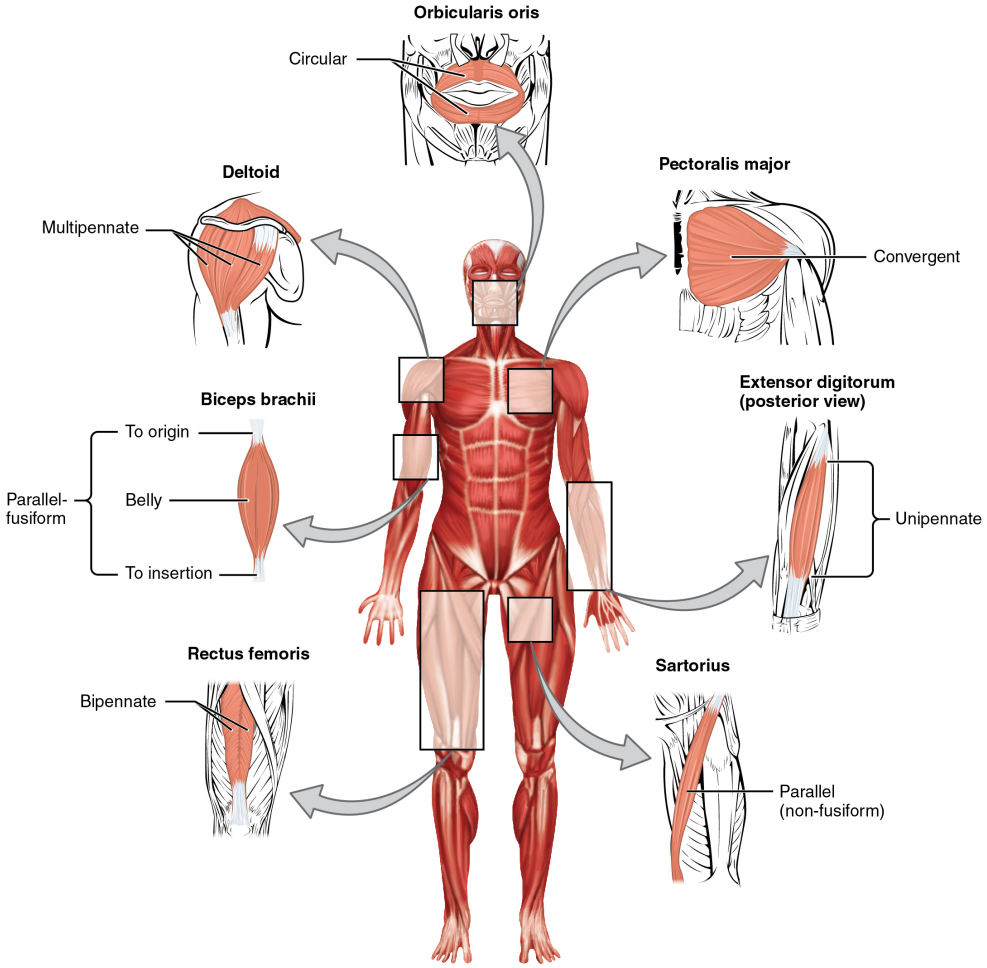


FIGURE 11.3 Muscle Shapes and Fiber Alignment The skeletal muscles of the body typically come in seven different general shapes.

Because of fascicles, a portion of a multipennate muscle like the deltoid can be stimulated by the nervous system to change the direction of the pull. For example, when the deltoid muscle contracts, the arm abducts (moves away from midline in the sagittal plane), but when only the anterior fascicle is stimulated, the arm will **abduct** and flex (move anteriorly at the shoulder joint).

The Lever System of Muscle and Bone Interactions

Skeletal muscles do not work by themselves. Muscles are arranged in pairs based on their functions. For muscles attached to the bones of the skeleton, the connection determines the force, speed, and range of movement. These characteristics depend on each other and can explain the general organization of the muscular and skeletal systems.

The skeleton and muscles act together to move the body. Have you ever used the back of a hammer to remove a nail from wood? The handle acts as a lever and the head of the hammer acts as a fulcrum, the fixed point that the force is applied to when you pull back or push down on the handle. The effort applied to this system is the pulling or pushing on the handle to remove the nail, which is the load, or "resistance" to the movement of the handle in the system. Our musculoskeletal system works in a similar manner, with bones being stiff levers and the articular endings of the bones—encased in synovial joints—acting as fulcrums. The load would be an object being lifted or any resistance to a movement (your head is a load when you are lifting it), and the effort, or applied force, comes from contracting skeletal muscle.

11.2 Naming Skeletal Muscles

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the criteria used to name skeletal muscles
- Explain how understanding the muscle names helps describe shapes, location, and actions of various muscles

The Greeks and Romans conducted the first studies done on the human body in Western culture. The educated class of subsequent societies studied Latin and Greek, and therefore the early pioneers of anatomy continued to apply Latin and Greek terminology or roots when they named the skeletal muscles. The large number of muscles in the body and unfamiliar words can make learning the names of the muscles in the body seem daunting, but understanding the etymology can help. Etymology is the study of how the root of a particular word entered a language and how the use of the word evolved over time. Taking the time to learn the root of the words is crucial to understanding the vocabulary of anatomy and physiology. When you understand the names of muscles it will help you remember where the muscles are located and what they do (Figure 11.5, Figure 11.6, and Table 11.2). Pronunciation of words and terms will take a bit of time to master, but after you have some basic information; the correct names and pronunciations will become easier.

superficial and deep muscles.

Example	Word	Latin Root 1	Latin Root 2	Meaning	Translation
abductor digiti minimi	abductor	ab = away from	duct = to move	a muscle that moves away from	A muscle that moves the little finger or toe away
	digiti	digitus = digit		refers to a finger or toe	
	minimi	minimus = mini, tiny		little	
adductor digiti minimi	adductor	ad = to, toward	duct = to move	a muscle that moves towards	A muscle that moves the little finger or toe toward
	digiti	digitus = digit		refers to a finger or toe	
	minimi	minimus = mini, tiny		little	

FIGURE 11.6 **Understanding a Muscle Name from the Latin**

Mnemonic Device for Latin Roots

Example	Latin or Greek Translation	Mnemonic Device
ad	to; toward	ADvance toward your goal
ab	away from	n/a
sub	under	SUBmarines move under water.
ductor	something that moves	A conDUCTOR makes a train move.
anti	against	If you are antisocial, you are against engaging in social activities.
epi	on top of	n/a
apo	to the side of	n/a
longissimus	longest	“Longissimus” is longer than the word “long.”
longus	long	long
brevis	short	brief
maximus	large	max
medius	medium	“Medius” and “medium” both begin with “med.”
minimus	tiny; little	mini
rectus	straight	To RECTify a situation is to straighten it out.
multi	many	If something is MULTIcolored, it has many colors.
uni	one	A UNIcorn has one horn.

TABLE 11.2

not move). The insertions of these muscles have fibers intertwined with connective tissue and the dermis of the skin. Because the muscles insert in the skin rather than on bone, when they contract, the skin moves to create facial expression (Figure 11.7).

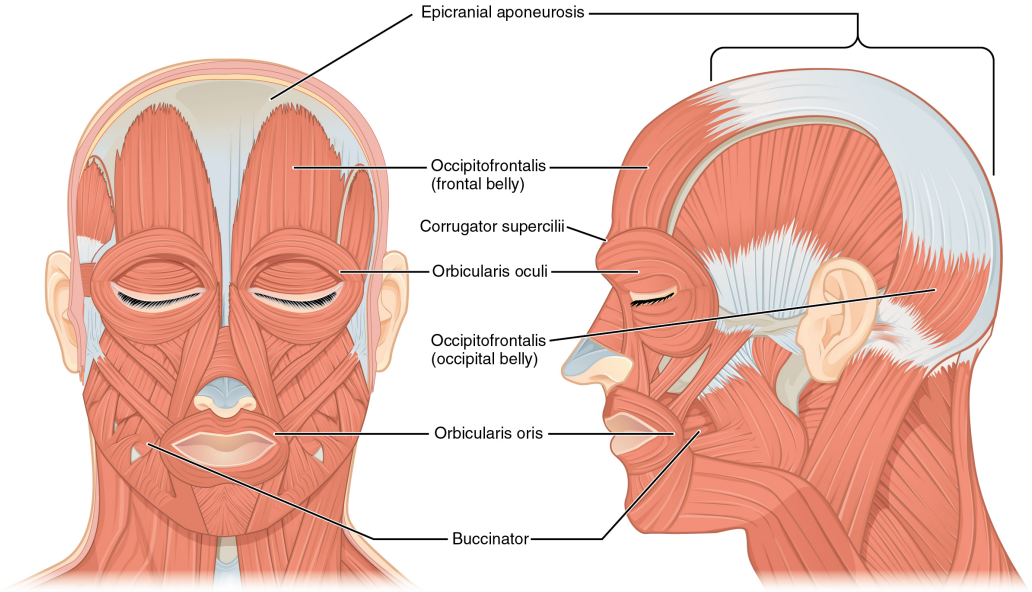


FIGURE 11.7 Muscles of Facial Expression Many of the muscles of facial expression insert into the skin surrounding the eyelids, nose and mouth, producing facial expressions by moving the skin rather than bones.

The **orbicularis oris** is a circular muscle that moves the lips, and the **orbicularis oculi** is a circular muscle that closes the eye. The **occipitofrontalis** muscle moves up the scalp and eyebrows. The muscle has a frontal belly and an occipital (near the occipital bone on the posterior part of the skull) belly. In other words, there is a muscle on the forehead (**frontalis**) and one on the back of the head (**occipitalis**), but there is no muscle across the top of the head. Instead, the two bellies are connected by a broad tendon called the **epicranial aponeurosis**, or galea aponeurosis (galea = "helmet"). The physicians originally studying human anatomy thought the skull looked like a helmet.

A large portion of the face is composed of the **buccinator** muscle, which compresses the cheek. This muscle allows you to whistle, blow, and suck; and it contributes to the action of chewing. There are several small facial muscles, one of which is the **corrugator supercilii**, which is the prime mover of the eyebrows. Place your finger on your eyebrows at the point of the bridge of the nose. Raise your eyebrows as if you were surprised and lower your eyebrows as if you were frowning. With these movements, you can feel the action of the corrugator supercilii. Additional muscles of facial expression are presented in Figure 11.8.

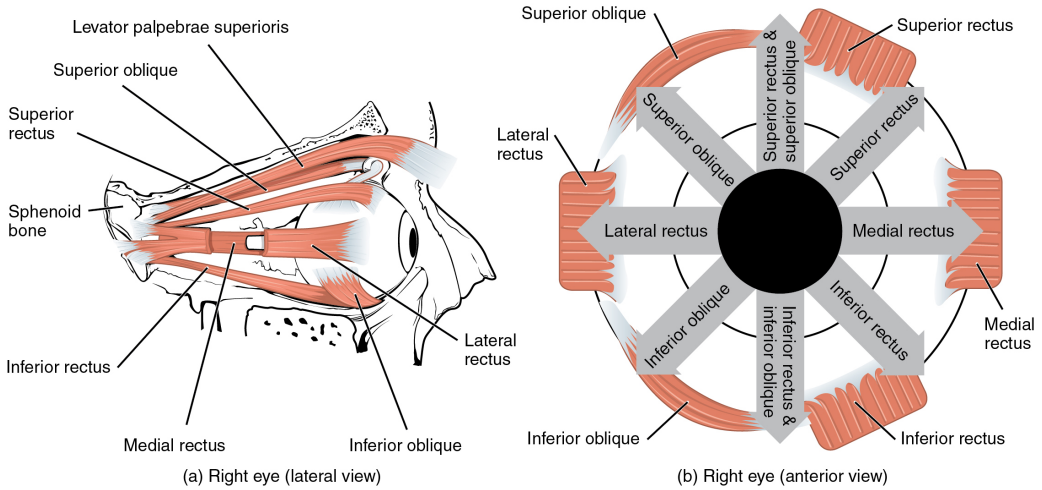


FIGURE 11.9 Muscles of the Eyes (a) The extrinsic eye muscles originate outside of the eye on the skull. (b) Each muscle inserts onto the eyeball.

Muscles of the Eyes

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Moves eyes up and toward nose; rotates eyes from 1 o'clock to 3 o'clock	Eyeballs	Superior (elevates); medial (adducts)	Superior rectus	Common tendinous ring (ring attaches to optic foramen)	Superior surface of eyeball
Moves eyes down and toward nose; rotates eyes from 6 o'clock to 3 o'clock	Eyeballs	Inferior (depresses); medial (adducts)	Inferior rectus	Common tendinous ring (ring attaches to optic foramen)	Inferior surface of eyeball
Moves eyes away from nose	Eyeballs	Lateral (abducts)	Lateral rectus	Common tendinous ring (ring attaches to optic foramen)	Lateral surface of eyeball
Moves eyes toward nose	Eyeballs	Medial (adducts)	Medial rectus	Common tendinous ring (ring attaches to optic foramen)	Medial surface of eyeball
Moves eyes up and away from nose; rotates eyeball from 12 o'clock to 9 o'clock	Eyeballs	Superior (elevates); lateral (abducts)	Inferior oblique	Floor of orbit (maxilla)	Surface of eyeball between inferior rectus and lateral rectus

TABLE 11.3

Muscles of the Lower Jaw

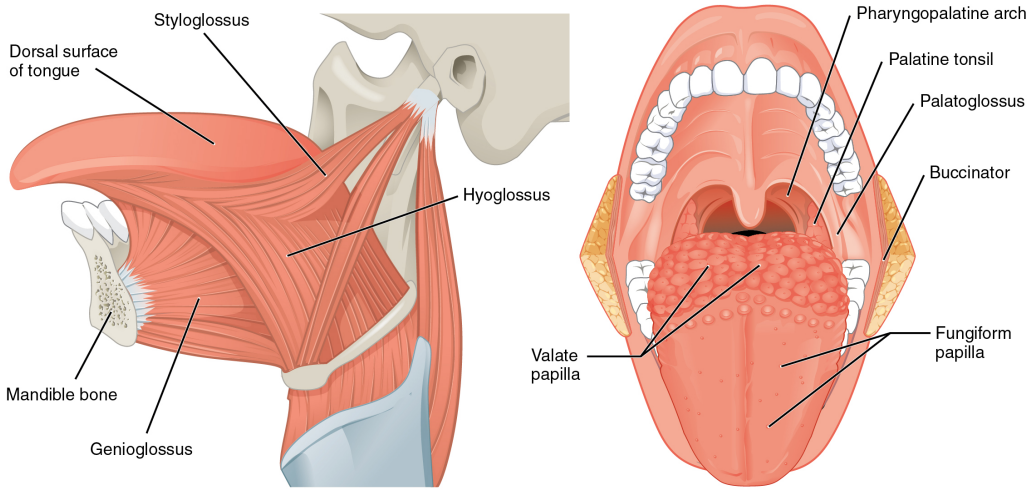
Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Closes mouth; aids chewing	Mandible	Superior (elevates)	Masseter	Maxilla arch; zygomatic arch (for masseter)	Mandible
Closes mouth; pulls lower jaw in under upper jaw	Mandible	Superior (elevates); posterior (retracts)	Temporalis	Temporal bone	Mandible
Opens mouth; pushes lower jaw out under upper jaw; moves lower jaw side-to-side	Mandible	Inferior (depresses); posterior (protracts); lateral (abducts); medial (adducts)	Lateral pterygoid	Pterygoid process of sphenoid bone	Mandible
Closes mouth; pushes lower jaw out under upper jaw; moves lower jaw side-to-side	Mandible	Superior (elevates); posterior (protracts); lateral (abducts); medial (adducts)	Medial pterygoid	Sphenoid bone; maxilla	Mandible; temporo-mandibular joint

TABLE 11.4

Although the masseter and temporalis are responsible for elevating and closing the jaw to break food into digestible pieces, the **medial pterygoid** and **lateral pterygoid** muscles provide assistance in chewing and moving food within the mouth.

Muscles That Move the Tongue

Although the tongue is obviously important for tasting food, it is also necessary for mastication, **deglutition** (swallowing), and speech (Figure 11.11 and Figure 11.12). Because it is so moveable, the tongue facilitates complex speech patterns and sounds.



(a) Extrinsic tongue muscles (b) Palatoglossus and surface of tongue

FIGURE 11.11 **Muscles that Move the Tongue**

Everyday Connection

Anesthesia and the Tongue Muscles

Before surgery, a patient must be made ready for general anesthesia. The normal homeostatic controls of the body are put "on hold" so that the patient can be prepped for surgery. Control of respiration must be switched from the patient's homeostatic control to the control of the anesthesiologist. The drugs used for anesthesia relax a majority of the body's muscles.

Among the muscles affected during general anesthesia are those that are necessary for breathing and moving the tongue. Under anesthesia, the tongue can relax and partially or fully block the airway, and the muscles of respiration may not move the diaphragm or chest wall. To avoid possible complications, the safest procedure to use on a patient is called endotracheal intubation. Placing a tube into the trachea allows the doctors to maintain a patient's (open) airway to the lungs and seal the airway off from the oropharynx. Post-surgery, the anesthesiologist gradually changes the mixture of the gases that keep the patient unconscious, and when the muscles of respiration begin to function, the tube is removed. It still takes about 30 minutes for a patient to wake up, and for breathing muscles to regain control of respiration. After surgery, most people have a sore or scratchy throat for a few days.

Muscles of the Anterior Neck

The muscles of the anterior neck assist in deglutition (swallowing) and speech by controlling the positions of the larynx (voice box), and the hyoid bone, a horseshoe-shaped bone that functions as a solid foundation on which the tongue can move. The muscles of the neck are categorized according to their position relative to the hyoid bone (Figure 11.13). **Suprahyoid muscles** are superior to it, and the **infrahyoid muscles** are located inferiorly.

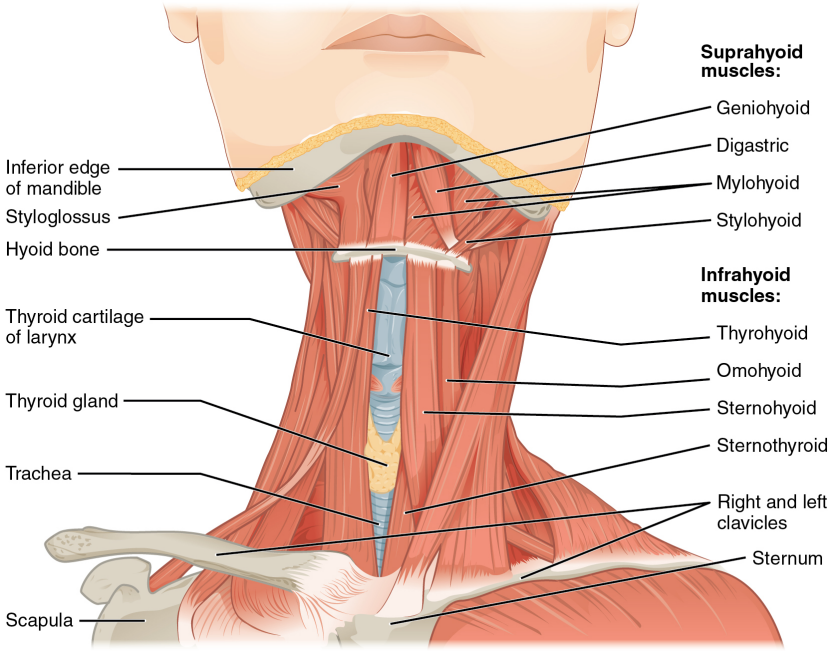


FIGURE 11.13 Muscles of the Anterior Neck The anterior muscles of the neck facilitate swallowing and speech. The suprahyoid muscles originate from above the hyoid bone in the chin region. The infrahyoid muscles originate below the hyoid bone in the lower neck.

The suprahyoid muscles raise the hyoid bone, the floor of the mouth, and the larynx during deglutition. These include the **digastric** muscle, which has anterior and posterior bellies that work to elevate the hyoid bone and larynx when one swallows; it also depresses the mandible. The **stylohyoid** muscle moves the hyoid bone posteriorly, elevating the larynx, and the **mylohyoid** muscle lifts it and helps press the tongue to the top of the mouth. The **geniohyoid** depresses the mandible in addition to raising and pulling the hyoid bone anteriorly.

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Rotates and tilts head to the side; tilts head backward	Skull; vertebrae	Individually: laterally flexes and rotates head to same side; bilaterally: extension	Splenius capitis	Spinous processes of cervical and thoracic vertebra	Temporal bone (mastoid process); occipital bone
Rotates and tilts head to the side; tilts head backward	Skull; vertebrae	Individually: laterally flexes and rotates head to same side; bilaterally: extension	Longissimus capitis	Transverse and articular processes of cervical and thoracic vertebra	Temporal bone (mastoid process)

TABLE 11.5

Muscles of the Posterior Neck and the Back

The posterior muscles of the neck are primarily concerned with head movements, like extension. The back muscles stabilize and move the vertebral column, and are grouped according to the lengths and direction of the fascicles.

The **splenius** muscles originate at the midline and run laterally and superiorly to their insertions. From the sides and the back of the neck, the **splenius capitis** inserts onto the head region, and the **splenius cervicis** extends onto the cervical region. These muscles can extend the head, laterally flex it, and rotate it (Figure 11.15).

the vertebral column.

Important in the stabilization of the vertebral column is the **segmental muscle group**, which includes the interspinales and intertransversarii muscles. These muscles bring together the spinous and transverse processes of each consecutive vertebra. Finally, the **scalene muscles** work together to flex, laterally flex, and rotate the head. They also contribute to deep inhalation. The scalene muscles include the **anterior scalene** muscle (anterior to the middle scalene), the **middle scalene** muscle (the longest, intermediate between the anterior and posterior scalenes), and the **posterior scalene** muscle (the smallest, posterior to the middle scalene).

11.4 Axial Muscles of the Abdominal Wall, and Thorax

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the intrinsic skeletal muscles of the back and neck, and the skeletal muscles of the abdominal wall and thorax
- Identify the movement and function of the intrinsic skeletal muscles of the back and neck, and the skeletal muscles of the abdominal wall and thorax

It is a complex job to balance the body on two feet and walk upright. The muscles of the vertebral column, thorax, and abdominal wall extend, flex, and stabilize different parts of the body's trunk. The deep muscles of the core of the body help maintain posture as well as carry out other functions. The brain sends out electrical impulses to these various muscle groups to control posture by alternate contraction and relaxation. This is necessary so that no single muscle group becomes fatigued too quickly. If any one group fails to function, body posture will be compromised.

Muscles of the Abdomen

There are four pairs of abdominal muscles that cover the anterior and lateral abdominal region and meet at the anterior midline. These muscles of the anterolateral abdominal wall can be divided into four groups: the external obliques, the internal obliques, the transversus abdominis, and the rectus abdominis (Figure 11.16 and Table 11.6).

Muscles of the Abdomen

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Twisting at waist; also bending to the side	Vertebral column	Supination; lateral flexion	External obliques; internal obliques	Ribs 5–12; ilium	Ribs 7–10; linea alba; ilium
Squeezing abdomen during forceful exhalations, defecation, urination, and childbirth	Abdominal cavity	Compression	Transversus abdominis	Ilium; ribs 5–10	Sternum; linea alba; pubis
Sitting up	Vertebral column	Flexion	Rectus abdominis	Pubis	Sternum; ribs 5 and 7
Bending to the side	Vertebral column	Lateral flexion	Quadratus lumborum	Ilium; ribs 5–10	Rib 12; vertebrae L1–L4

TABLE 11.6

There are three flat skeletal muscles in the antero-lateral wall of the abdomen. The **external oblique**, closest to the surface, extend inferiorly and medially, in the direction of sliding one's four fingers into pants pockets. Perpendicular to it is the intermediate **internal oblique**, extending superiorly and medially, the direction the thumbs usually go when the other fingers are in the pants pocket. The deep muscle, the **transversus abdominis**, is arranged transversely around the abdomen, similar to the front of a belt on a pair of pants. This arrangement of three bands of muscles in different orientations allows various movements and rotations of the trunk. The three layers of muscle also help to protect the internal abdominal organs in an area where there is no bone.

The **linea alba** is a white, fibrous band that is made of the bilateral **rectus sheaths** that join at the anterior midline of the body. These enclose the **rectus abdominis** muscles (a pair of long, linear muscles, commonly called the "sit-up" muscles) that originate at the pubic crest and symphysis, and extend the length of the body's trunk. Each muscle is segmented by three transverse bands of collagen fibers called the **tendinous intersections**. This results in the look of "six-pack abs," as each segment hypertrophies on individuals at the gym who do many sit-ups.

The posterior abdominal wall is formed by the lumbar vertebrae, parts of the ilia of the hip bones, psoas major and iliacus muscles, and **quadratus lumborum** muscle. This part of the core plays a key role in stabilizing the rest of the body and maintaining posture.

CAREER CONNECTION

Physical Therapists

Those who have a muscle or joint injury will most likely be sent to a physical therapist (PT) after seeing their regular doctor. PTs have a master's degree or doctorate, and are highly trained experts in the mechanics of body movements. Many PTs also specialize in sports injuries.

If you injured your shoulder while you were kayaking, the first thing a physical therapist would do during your first visit is to assess the functionality of the joint. The range of motion of a particular joint refers to the normal movements the joint performs. The PT will ask you to abduct and adduct, circumduct, and flex and extend the arm. The PT will note the shoulder's degree of function, and based on the assessment of the injury, will create an

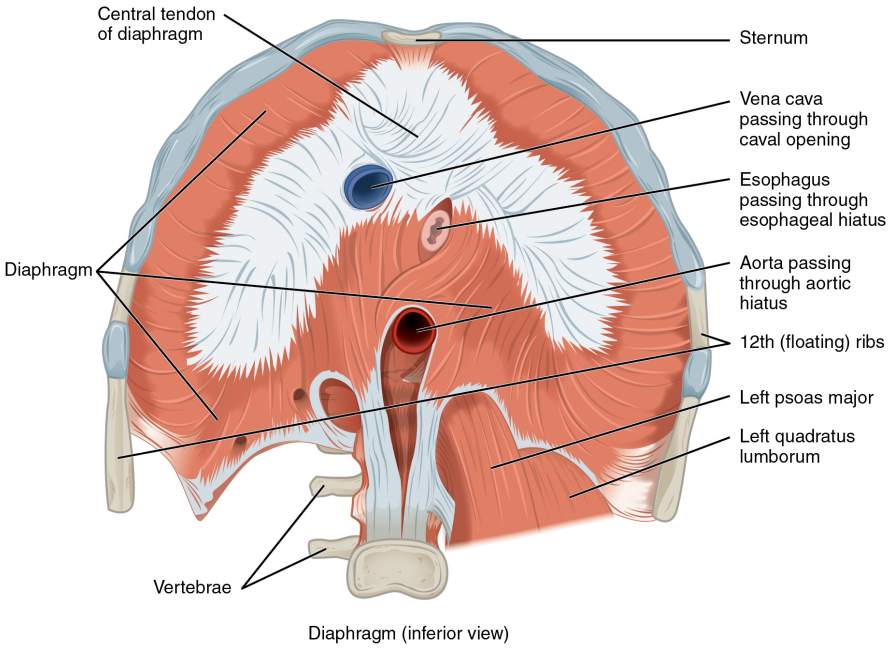


FIGURE 11.17 Muscles of the Diaphragm The diaphragm separates the thoracic and abdominal cavities.

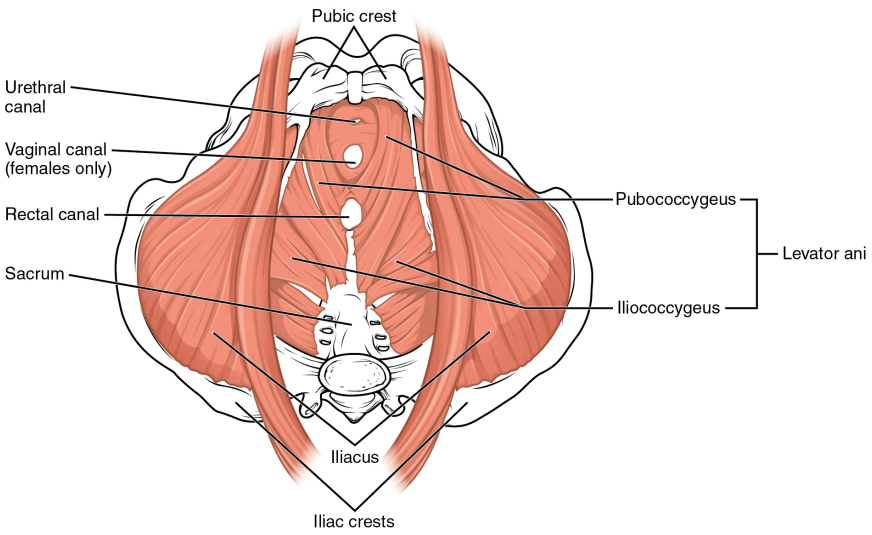
Defecating, urination, and even childbirth involve cooperation between the diaphragm and abdominal muscles (this cooperation is referred to as the "Valsalva maneuver"). You hold your breath by a steady contraction of the diaphragm; this stabilizes the volume and pressure of the peritoneal cavity. When the abdominal muscles contract, the pressure cannot push the diaphragm up, so it increases pressure on the intestinal tract (defecation), urinary tract (urination), or reproductive tract (childbirth).

The inferior surface of the pericardial sac and the inferior surfaces of the pleural membranes (parietal pleura) fuse onto the central tendon of the diaphragm. To the sides of the tendon are the skeletal muscle portions of the diaphragm, which insert into the tendon while having a number of origins including the xiphoid process of the sternum anteriorly, the inferior six ribs and their cartilages laterally, and the lumbar vertebrae and 12th ribs posteriorly.

The diaphragm also includes three openings for the passage of structures between the thorax and the abdomen. The inferior vena cava passes through the **caval opening**, and the esophagus and attached nerves pass through the esophageal hiatus. The aorta, thoracic duct, and azygous vein pass through the aortic hiatus of the posterior diaphragm.

The Intercostal Muscles

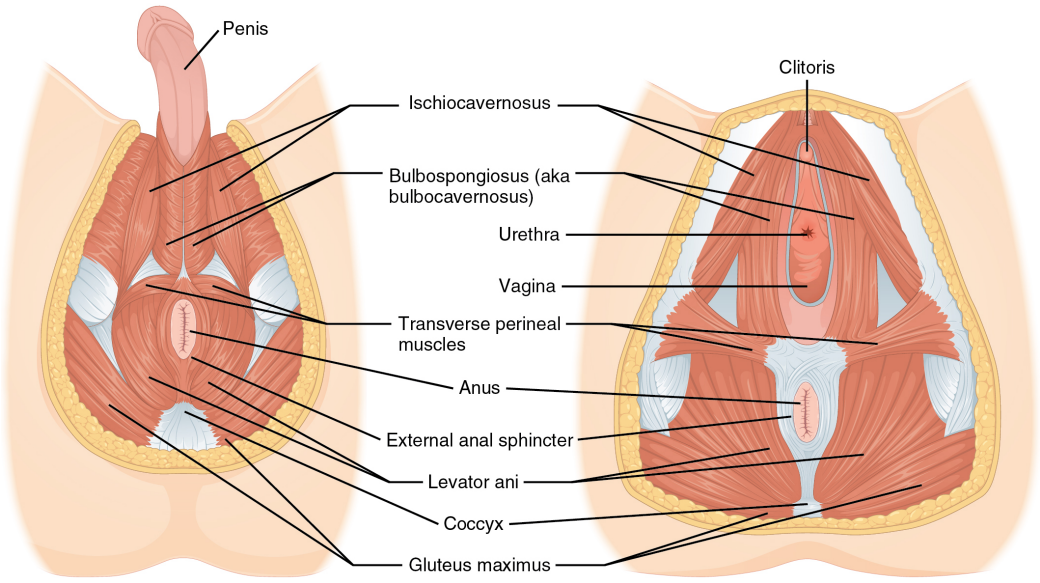
There are three sets of muscles, called **intercostal muscles**, which span each of the intercostal spaces. The principal role of the intercostal muscles is to assist in breathing by changing the dimensions of the rib cage (Figure 11.18).



Pelvic diaphragm (superior view)

FIGURE 11.19 Muscles of the Pelvic Floor The pelvic floor muscles support the pelvic organs, resist intra-abdominal pressure, and work as sphincters for the urethra, rectum, and vagina.

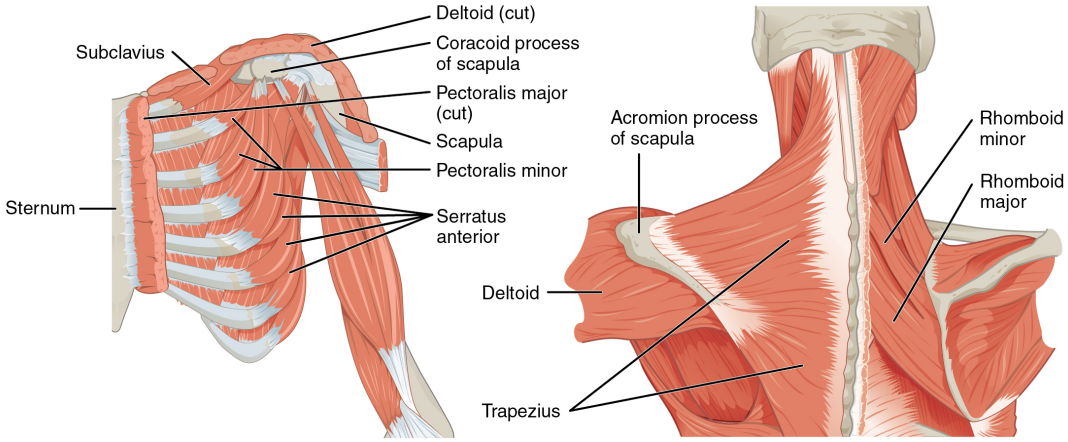
The **perineum** is the diamond-shaped space between the pubic symphysis (anteriorly), the coccyx (posteriorly), and the ischial tuberosities (laterally), lying just inferior to the pelvic diaphragm (levator ani and coccygeus). Divided transversely into triangles, the anterior is the **urogenital triangle**, which includes the external genitals. The posterior is the **anal triangle**, which contains the anus (Figure 11.20). The perineum is also divided into superficial and deep layers with some of the muscles common to people of any sex (Figure 11.21). Females also have the **compressor urethrae** and the **sphincter urethrovaginalis**, which function to close the vagina. In males, there is the **deep transverse perineal** muscle that plays a role in ejaculation.



Male perineal muscles: inferior view

Female perineal muscles: inferior view

FIGURE 11.20 Muscles of the Perineum The perineum muscles play roles in urination in both sexes, ejaculation in males, and vaginal contraction in females.



Pectoral girdle muscle (left anterior lateral view) Pectoral girdle muscles (posterior view)

FIGURE 11.22 Muscles That Position the Pectoral Girdle The muscles that stabilize the pectoral girdle make it a steady base on which other muscles can move the arm. Note that the pectoralis major and deltoid, which move the humerus, are cut here to show the deeper positioning muscles.

Muscles that Position the Pectoral Girdle

Position in the thorax	Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Anterior thorax	Stabilizes clavicle during movement by depressing it	Clavicle	Depression	Subclavius	First rib	Inferior surface of clavicle
Anterior thorax	Rotates shoulder anteriorly (throwing motion); assists with inhalation	Scapula; ribs	Scapula: depresses; ribs: elevates	Pectoralis minor	Anterior surfaces of certain ribs (2–4 or 3–5)	Coracoid process of scapula
Anterior thorax	Moves arm from side of body to front of body; assists with inhalation	Scapula; ribs	Scapula: protracts; ribs: elevates	Serratus anterior	Muscle slips from certain ribs (1–8 or 1–9)	Anterior surface of vertebral border of scapula
Posterior thorax	Elevates shoulders (shrugging); pulls shoulder blades together; tilts head backwards	Scapula; cervical spine	Scapula: rotests inferiorly, retracts, elevates, and depresses; spine: extends	Trapezius	Skull; vertebral column	Acromion and spine of scapula; clavicle

TABLE 11.8

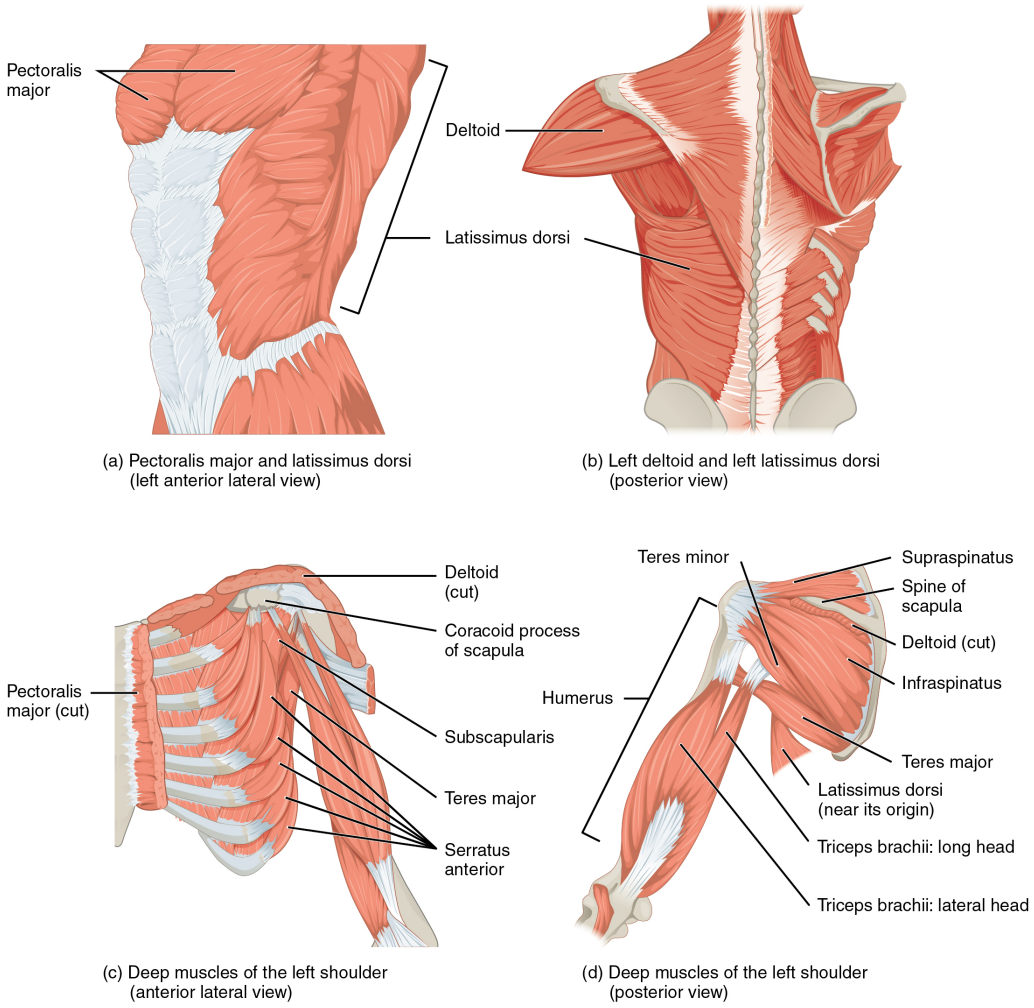


FIGURE 11.23 Muscles That Move the Humerus (a, c) The muscles that move the humerus anteriorly are generally located on the anterior side of the body and originate from the sternum (e.g., pectoralis major) or the anterior side of the scapula (e.g., subscapularis). (b) The muscles that move the humerus superiorly generally originate from the superior surfaces of the scapula and/or the clavicle (e.g., deltoids). The muscles that move the humerus inferiorly generally originate from middle or lower back (e.g., latissiumus dorsi). (d) The muscles that move the humerus posteriorly are generally located on the posterior side of the body and insert into the scapula (e.g., infraspinatus).

flexion, extension, pronation, and supination. The forearm flexors include the biceps brachii, brachialis, and brachioradialis. The extensors are the **triceps brachii** and **anconeus**. The pronators are the **pronator teres** and the **pronator quadratus**, and the **supinator** is the only one that turns the forearm anteriorly. When the forearm faces anteriorly, it is supinated. When the forearm faces posteriorly, it is pronated.

The biceps brachii, brachialis, and brachioradialis flex the forearm. The two-headed **biceps brachii** crosses the shoulder and elbow joints to flex the forearm, also taking part in supinating the forearm at the radioulnar joints and flexing the arm at the shoulder joint. Deep to the biceps brachii, the **brachialis** provides additional power in flexing the forearm. Finally, the **brachioradialis** can flex the forearm quickly or help lift a load slowly. These muscles and their associated blood vessels and nerves form the **anterior compartment of the arm** (anterior flexor compartment of the arm) (Figure 11.25 and Figure 11.26).

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Anterior muscles (flexion)					
Performs a bicep curl; also allows palm of hand to point toward body while flexing	Forearm	Flexion; supination	Biceps brachii	Coracoid process; tubercle above glenoid cavity	Radial tuberosity
	Forearm	Flexion	Brachialis	Front of distal humerus	Coronoid process of ulna
Assists and stabilizes elbow during bicep-curl motion	Forearm	Flexion	Brachioradialis	Lateral supracondylar ridge at distal end of humerus	Base of styloid process of radius
Posterior muscles (extension)					
Extends forearm, as during a punch	Forearm	Extension	Triceps brachii	Infraglenoid tubercle of scapula; posterior shaft of humerus; posterior humeral shaft distal to radial groove	Olecranon process of ulna
Assists in extending forearm; also allows forearm to extend away from body	Forearm	Extension; abduction	Anconeus	Lateral epicondyle of humerus	Lateral aspect of olecranon process of ulna
Anterior muscles (pronation)					
Turns hand palm-down	Forearm	Pronation	Pronator teres	Medial epicondyle of humerus; coronoid process of ulna	Lateral radius
Assists in turning hand palm-down	Forearm	Pronation	Pronator quadratus	Distal portion of anterior ulnar shaft	Distal surface of anterior radius
Posterior muscles (supination)					
Turns hand palm-up	Forearm	Supination	Supinator	Lateral epicondyle of humerus; proximal ulna	Proximal end of radius

FIGURE 11.26 **Muscles That Move the Forearm**

Muscles That Move the Wrist, Hand, and Fingers

Wrist, hand, and finger movements are facilitated by two groups of muscles. The forearm is the origin of the **extrinsic muscles of the hand**. The palm is the origin of the intrinsic muscles of the hand.

Muscles of the Arm That Move the Wrists, Hands, and Fingers

The muscles in the **anterior compartment of the forearm** (anterior flexor compartment of the forearm) originate on the humerus and insert onto different parts of the hand. These make up the bulk of the forearm. From lateral to medial, the **superficial anterior compartment of the forearm** includes the **flexor carpi radialis**, **palmaris longus**, **flexor carpi ulnaris**, and **flexor digitorum superficialis**. The flexor digitorum superficialis flexes the hand as well as the digits at the knuckles, which allows for rapid finger movements, as in typing or playing a musical instrument (see Figure 11.27 and Table 11.9). However, poor ergonomics can irritate the tendons of these muscles as they slide back and forth with the carpal tunnel of the anterior wrist and pinch the median nerve, which also travels through the tunnel, causing Carpal Tunnel Syndrome. The **deep anterior compartment** produces flexion and bends fingers to make a fist. These are the **flexor pollicis longus** and the **flexor digitorum profundus**.

The muscles in the **superficial posterior compartment of the forearm** (superficial posterior extensor compartment of the forearm) originate on the humerus. These are the **extensor radialis longus**, **extensor carpi radialis brevis**, **extensor digitorum**, **extensor digiti minimi**, and the **extensor carpi ulnaris**.

The muscles of the **deep posterior compartment of the forearm** (deep posterior extensor compartment of the forearm) originate on the radius and ulna. These include the **abductor pollicis longus**, **extensor pollicis brevis**,

groups. The **thenar** muscles are on the radial aspect of the palm. The **hypothenar** muscles are on the medial aspect of the palm, and the **intermediate** muscles are midpalmar.

The thenar muscles include the **abductor pollicis brevis**, **opponens pollicis**, **flexor pollicis brevis**, and the **adductor pollicis**. These muscles form the **thenar eminence**, the rounded contour of the base of the thumb, and all act on the thumb. The movements of the thumb play an integral role in most precise movements of the hand.

The hypothenar muscles include the **abductor digiti minimi**, **flexor digiti minimi brevis**, and the **opponens digiti minimi**. These muscles form the **hypothenar eminence**, the rounded contour of the little finger, and as such, they all act on the little finger. Finally, the intermediate muscles act on all the fingers and include the **lumbrical**, the **palmar interossei**, and the **dorsal interossei**.

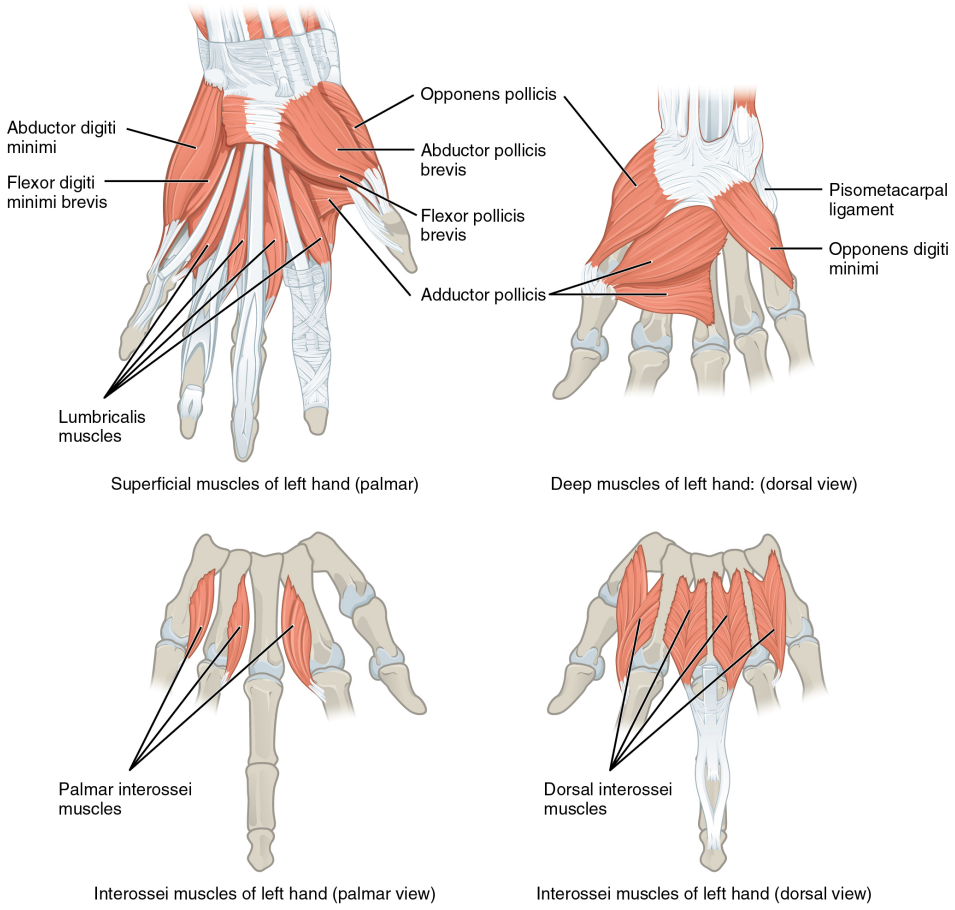


FIGURE 11.28 Intrinsic Muscles of the Hand The intrinsic muscles of the hand both originate and insert within the hand. These muscles provide the fine motor control of the fingers by flexing, extending, abducting, and adducting the more distal finger and thumb segments.

Muscle	Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Intermediate muscles	Adducts and flexes each finger at metacarpo-phalangeal joints; extends each finger at interphalangeal joints	Fingers	Adduction; flexion; extension	Palmar interossei	Side of each metacarpal that faces metacarpal 3 (absent from metacarpal 3)	Extensor expansion on first phalanx of each finger (except finger 3) on side facing finger 3
Intermediate muscles	Abducts and flexes the three middle fingers at metacarpo-phalangeal joints; extends the three middle fingers at interphalangeal joints	Fingers	Abduction; flexion; extension	Dorsal interossei	Sides of metacarpals	Both sides of finger 3; for each other finger, extensor expansion over first phalanx on side opposite finger 3

TABLE 11.9

11.6 Appendicular Muscles of the Pelvic Girdle and Lower Limbs

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the appendicular muscles of the pelvic girdle and lower limb
- Identify the movement and function of the pelvic girdle and lower limb

The appendicular muscles of the lower body position and stabilize the **pelvic girdle**, which serves as a foundation for the lower limbs. Comparatively, there is much more movement at the pectoral girdle than at the pelvic girdle. There is very little movement of the pelvic girdle because of its connection with the sacrum at the base of the axial skeleton. The pelvic girdle is less range of motion because it was designed to stabilize and support the body.

Muscles of the Thigh

What would happen if the pelvic girdle, which attaches the lower limbs to the torso, were capable of the same range of motion as the pectoral girdle? For one thing, walking would expend more energy if the heads of the femurs were not secured in the acetabula of the pelvis. The body's center of gravity is in the area of the pelvis. If the center of gravity were not to remain fixed, standing up would be difficult as well. Therefore, what the leg muscles lack in range of motion and versatility, they make up for in size and power, facilitating the body's stabilization, posture, and movement.

Gluteal Region Muscles That Move the Femur

Most muscles that insert on the femur (the thigh bone) and move it, originate on the pelvic girdle. The **psoas major** and **iliacus** make up the **iliopsoas group**. Some of the largest and most powerful muscles in the body are the gluteal muscles or **gluteal group**. The **gluteus maximus** is the largest; deep to the gluteus maximus is the **gluteus medius**, and deep to the gluteus medius is the **gluteus minimus**, the smallest of the trio (Figure 11.29 and Figure 11.30).

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Iliopsoas group					
Raises knee at hip, as if performing a knee attack; assists lateral rotators in twisting thigh (and lower leg) outward; assists with bending over, maintaining posture	Femur	Thigh: flexion and lateral rotation; torso: flexion	Psoas major	Lumbar vertebrae (L1–L5); thoracic vertebra (T12)	Lesser trochanter of femur
Raises knee at hip, as if performing a knee attack; assists lateral rotators in twisting thigh (and lower leg) outward; assists with bending over, maintaining posture	Femur	Thigh: flexion and lateral rotation; torso: flexion	Iliacus	Iliac fossa; iliac crest; lateral sacrum	Lesser trochanter of femur
Gluteal group					
Lowers knee and moves thigh back, as when getting ready to kick a ball	Femur	Extension	Gluteus maximus	Dorsal ilium; sacrum; coccyx	Gluteal tuberosity of femur; iliotibial tract
Opens thighs, as when doing a split	Femur	Abduction	Gluteus medius	Lateral surface of ilium	Greater trochanter of femur
Brings the thighs back together	Femur	Abduction	Gluteus minimus	External surface of ilium	Greater trochanter of femur
Assists with raising knee at hip and opening thighs; maintains posture by stabilizing the iliotibial track, which connects to the knee	Femur	Flexion; abduction	Tensor fascia lata	Anterior aspect of iliac crest; anterior superior iliac spine	Iliotibial tract
Lateral rotators					
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Piriformis	Anterolateral surface of sacrum	Greater trochanter of femur
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Obutrator internus	Inner surface of obturator membrane; greater sciatic notch; margins of obturator foramen	Greater trochanter in front of piriformis
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Obturator externus	Outer surfaces of obturator membrane, pubic, and ischium; margins of obturator foramen	Trochanteric fossa of posterior femur
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Superior gemellus	Ischial spine	Greater trochanter of femur
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Inferior gemellus	Ischial tuberosity	Greater trochanter of femur
Twists thigh (and lower leg) outward; maintains posture by stabilizing hip joint	Femur	Lateral rotation	Quadratus femoris	Ischial tuberosity	Trochanteric crest of femur
Adductors					
Brings the thighs back together; assists with raising the knee	Femur	Adduction; flexion	Adductor longus	Pubis near pubic symphysis	Linea aspera
Brings the thighs back together; assists with raising the knee	Femur	Adduction; flexion	Adductor brevis	Body of pubis; inferior ramus of pubis	Linea aspera above adductor longus
Brings the thighs back together; assists with raising the knee and moving the thigh back	Femur	Adduction; flexion; extension	Adductor magnus	Ischial rami; pubic rami; ischial tuberosity	Linea aspera; adductor tubercle of femur
Opens thighs; assists with raising the knee and turning the thigh (and lower leg) inward	Femur	Adduction; flexion; medial rotation	Pectineus	Pectineal line of pubis	Lesser trochanter to linea aspera of posterior aspect of femur

FIGURE 11.30 **Gluteal Region Muscles That Move the Femur**

The **tensor fascia latae** is a thick, squarish muscle in the superior aspect of the lateral thigh. It acts as a synergist of the gluteus medius and iliopsoas in flexing and abducting the thigh. It also helps stabilize the lateral aspect of the

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Medial compartment of thigh					
Moves back of lower legs up toward buttocks, as when kneeling; assists in opening thighs	Femur; tibia/fibula	Tibia/fibula: flexion; thigh: adduction	Gracilis	Inferior ramus; body of pubis; ischial ramus	Medial surface of tibia
Anterior compartment of thigh: Quadriceps femoris group					
Moves lower leg out in front of body, as when kicking; assists in raising the knee	Femur; tibia/fibula	Tibia/fibula: extension; thigh: flexion	Rectus femoris	Anterior inferior iliac spine; superior margin of acetabulum	Patella; tibial tuberosity
Moves lower leg out in front of body, as when kicking	Tibia/fibula	Extension	Vastus lateralis	Greater trochanter; intertrochanteric line; linea aspera	Patella; tibial tuberosity
Moves lower leg out in front of body, as when kicking	Tibia/fibula	Extension	Vastus medialis	Linea aspera; intertrochanteric line	Patella; tibial tuberosity
Moves lower leg out in front of body, as when kicking	Tibia/fibula	Extension	Vastus intermedius	Proximal femur shaft	Patella; tibial tuberosity
Moves back of lower legs up and back toward the buttocks, as when kneeling; assists in moving thigh diagonally upward and outward as when mounting a bike	Femur; tibia/fibula	Tibia: flexion; thigh: flexion, abduction, lateral rotation	Sartorius	Anterior superior iliac spine	Medial aspect of proximal tibia
Posterior compartment of thigh: Hamstring group					
Moves back of lower legs up and back toward the buttocks, as when kneeling; moves thigh down and back; twists the thigh (and lower leg) outward	Femur; tibia/fibula	Tibia/fibula: flexion; thigh: extension, lateral rotation	Biceps femoris	Ischial tuberosity; linea aspera; distal femur	Head of fibula; lateral condyle of tibia
Moves back of lower legs up toward buttocks, as when kneeling; moves thigh down and back; twists the thigh (and lower leg) inward	Femur; tibia/fibula	Tibia/fibula: flexion; thigh: extension, medial rotation	Semitendinosus	Ischial tuberosity	Upper tibial shaft
Moves back of lower legs up and back toward the buttocks as when kneeling; moves thigh down and back; twists the thigh (and lower leg) inward	Femur; tibia/fibula	Tibia/fibula: flexion; thigh: extension, medial rotation	Semi-membranosus	Ischial tuberosity	Medial condyle of tibia; lateral condyle of femur

FIGURE 11.31 **Thigh Muscles That Move the Femur, Tibia, and Fibula**

The muscles of the **anterior compartment of the thigh** flex the thigh and extend the leg. This compartment contains the **quadriceps femoris group**, which actually comprises four muscles that extend and stabilize the knee. The **rectus femoris** is on the anterior aspect of the thigh, the **vastus lateralis** is on the lateral aspect of the thigh, the **vastus medialis** is on the medial aspect of the thigh, and the **vastus intermedius** is between the vastus lateralis and vastus medialis and deep to the rectus femoris. The tendon common to all four is the **quadriceps tendon** (patellar tendon), which inserts into the patella and continues below it as the **patellar ligament**. The patellar ligament attaches to the tibial tuberosity. In addition to the quadriceps femoris, the **sartorius** is a band-like muscle that extends from the anterior superior iliac spine to the medial side of the proximal tibia. This versatile muscle flexes the leg at the knee and flexes, abducts, and laterally rotates the leg at the hip. This muscle allows us to sit

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Anterior compartment of leg					
Raises the sole of the foot off the ground, as when preparing to foot-tap; bends the inside of the foot upwards, as when catching your balance while falling laterally toward the opposite side as the balancing foot	Foot	Dorsiflexion; inversion	Tibialis anterior	Lateral condyle and upper tibial shaft; interosseous membrane	Interior surface of medial cuneiform; First metatarsal bone
Raises the sole of the foot off the ground, as when preparing to foot-tap; extends the big toe	Foot; big toe	Foot: dorsiflexion; big toe: extension	Extensor hallucis longus	Anteromedial fibula shaft; interosseous membrane	Distal phalanx of big toe
Raises the sole of the foot off the ground, as when preparing to foot-tap; extends toes	Foot; toes 2–5	Foot: dorsiflexion; toes: extension	Extensor digitorum longus	Lateral condyle of tibia; proximal portion of fibula; interosseous membrane	Middle and distal phalanges of toes 2–5
Lateral compartment of leg					
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; bends the inside of the foot downwards, as when catching your balance while falling laterally toward the same side as the balancing foot	Foot	Plantar flexion and eversion	Fibularis longus	Upper portion of lateral fibula	First metatarsal; medial cuneiform
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; bends the inside of the foot downward, as when catching your balance while falling laterally toward the same side as the balancing foot	Foot	Plantar flexion and eversion	Fibularis (peroneus) brevis	Distal fibula shaft	Proximal end of fifth metatarsal
Posterior compartment of leg: Superficial muscles					
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; assists in moving the back of the lower legs up and back toward the buttocks	Foot; tibia/ fibula	Foot: plantar flexion; tibia/fibula: flexion	Gastrocnemius	Medial and lateral condyles of femur	Posterior calcaneus
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; maintains posture while walking	Foot	Plantar flexion	Soleus	Superior tibia; fibula; interosseous membrane	Posterior calcaneus
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; assists in moving the back of the lower legs up and back toward the buttocks	Foot; tibia/ fibula	Foot: plantar flexion; tibia/fibula: flexion	Plantaris	Posterior femur above lateral condyle	Calcaneus or calcaneus tendon
Lowers the sole of the foot to the ground, as when foot-tapping or jumping	Foot	Plantar flexion	Tibialis posterior	Superior tibia and fibula; interosseous membrane	Several tarsals and metatarsals 2–4
Posterior compartment of leg: Deep muscles					
Moves the back of the lower legs up and back toward the buttocks; assists in rotation of the leg at the knee and thigh	Tibia/ fibula	Tibia/fibula: flexion thigh and lower leg: medial and lateral rotation	Popliteus	Lateral condyle of femur; lateral meniscus	Proximal tibia
Lowers the sole of the foot to the ground, as when foot-tapping or jumping; bends the inside of the foot upward and flexes toes	Foot; toes 2–5	Foot: plantar flexion and inversion toes: flexion	Flexor digitorum longus	Posterior tibia	Distal phalanges of toes 2–5
Flexes the big toe	Big toe; foot	Big toe: flexion foot: plantar flexion	Flexor hallucis longus	Midshaft of fibula; interosseous membrane	Distal phalanx of big toe

FIGURE 11.33 **Muscles That Move the Feet and Toes**

The muscles in the **anterior compartment of the leg**: the **tibialis anterior**, a long and thick muscle on the lateral surface of the tibia, the **extensor hallucis longus**, deep under it, and the **extensor digitorum longus**, lateral to it, all contribute to raising the front of the foot when they contract. The **fibularis tertius**, a small muscle that originates on the anterior surface of the fibula, is associated with the extensor digitorum longus and sometimes fused to it, but is not present in all people. Thick bands of connective tissue called the **superior extensor retinaculum** (transverse ligament of the ankle) and the **inferior extensor retinaculum**, hold the tendons of these muscles in place during dorsiflexion.

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Dorsal group					
Extends toes 2–5	Toes 2–5	Extension	Extensor digitorum brevis	Calcaneus; extensor retinaculum	Base of proximal phalanx of big toe; extensor expansions on toes 2–5
Plantar group (layer 1)					
Abducts and flexes big toe	Big toe	Adduction; flexion	Abductor hallucis	Calcaneal tuberosity; flexor retinaculum	Proximal phalanx of big toe
Flexes toes 2–4	Middle toes	Flexion	Flexor digitorum brevis	Calcaneal tuberosity	Middle phalanx of toes 2–4
Abducts and flexes small toe	Toe 5	Abduction; flexion	Abductor digiti minimi	Calcaneal tuberosity	Proximal phalanx of little toe
Plantar group (layer 2)					
Assists in flexing toes 2–5	Toes 2–5	Flexion	Quadratus plantae	Medial and lateral sides of calcaneus	Tendon of flexor digitorum longus
Extends toes 2–5 at the interphalangeal joints; flexes the small toes at the metatarsophalangeal joints	Toes 2–5	Extension; flexion	Lumbricals	Tendons of flexor digitorum longus	Medial side of proximal phalanx of toes 2–5
Plantar group (layer 3)					
Flexes big toe	Big toe	Flexion	Flexor hallucis brevis	Lateral cuneiform; cuboid bones	Base of proximal phalanx of big toe
Adducts and flexes big toe	Big toe	Adduction; flexion	Adductor hallucis	Bases of metatarsals 2–4; fibularis longus tendon sheath; ligament across metatarsophalangeal joints	Base of proximal phalanx of big toe
Flexes small toe	Little toe	Flexion	Flexor digiti minimi brevis	Base of metatarsal 5; tendon sheath of fibularis longus	Base of proximal phalanx of little toe
Plantar group (layer 4)					
Abducts and flexes middle toes at metatarsophalangeal joints; extends middle toes at interphalangeal joints	Middle toes	Abduction; flexion; extension	Dorsal interossei	Sides of metatarsals	Both sides of toe 2; for each other toe, extensor expansion over first phalanx on side opposite toe 2
Abducts toes 3–5; flexes proximal phalanges and extends distal phalanges	Small toes	Abduction; flexion; extension	Plantar interossei	Side of each metatarsal that faces metatarsal 2 (absent from metatarsal 2)	Extensor expansion on first phalanx of each toe (except to 2) on side facing toe 2

FIGURE 11.35 **Intrinsic Muscles in the Foot**

extensor muscle that increases the angle at the joint
extensor carpi radialis brevis muscle that extends and abducts the hand at the wrist
extensor carpi ulnaris muscle that extends and adducts the hand
extensor digiti minimi muscle that extends the little finger
extensor digitorum muscle that extends the hand at the wrist and the phalanges
extensor digitorum brevis muscle that extends the toes
extensor digitorum longus muscle that is lateral to the tibialis anterior
extensor hallucis longus muscle that is partly deep to the tibialis anterior and extensor digitorum longus
extensor indicis muscle that inserts onto the tendon of the extensor digitorum of the index finger
extensor pollicis brevis muscle that inserts onto the base of the proximal phalanx of the thumb
extensor pollicis longus muscle that inserts onto the base of the distal phalanx of the thumb
extensor radialis longus muscle that extends and abducts the hand at the wrist
extensor retinaculum band of connective tissue that extends over the dorsal surface of the hand
external intercostal superficial intercostal muscles that raise the rib cage
external oblique superficial abdominal muscle with fascicles that extend inferiorly and medially
extrinsic eye muscles originate outside the eye and insert onto the outer surface of the white of the eye, and create eyeball movement
extrinsic muscles of the hand muscles that move the wrists, hands, and fingers and originate on the arm
fascicle muscle fibers bundled by perimysium into a unit
femoral triangle region formed at the junction between the hip and the leg and includes the pectineus, femoral nerve, femoral artery, femoral vein, and deep inguinal lymph nodes
fibularis brevis (also, peroneus brevis) muscle that plantar flexes the foot at the ankle and everts it at the intertarsal joints
fibularis longus (also, peroneus longus) muscle that plantar flexes the foot at the ankle and everts it at the intertarsal joints
fibularis tertius small muscle that is associated with the extensor digitorum longus
fixator synergist that assists an agonist by preventing or reducing movement at another joint, thereby stabilizing the origin of the agonist
flexion movement that decreases the angle of a joint
flexor muscle that decreases the angle at the joint
flexor carpi radialis muscle that flexes and abducts the hand at the wrist
flexor carpi ulnaris muscle that flexes and adducts the hand at the wrist
flexor digiti minimi brevis muscle that flexes the little finger
flexor digitorum longus muscle that flexes the four small toes
flexor digitorum profundus muscle that flexes the phalanges of the fingers and the hand at the wrist
flexor digitorum superficialis muscle that flexes the hand and the digits
flexor hallucis longus muscle that flexes the big toe
flexor pollicis brevis muscle that flexes the thumb
flexor pollicis longus muscle that flexes the distal phalanx of the thumb
flexor retinaculum band of connective tissue that extends over the palmar surface of the hand
frontalis front part of the occipitofrontalis muscle
fusiform muscle that has fascicles that are spindle-shaped to create large bellies
gastrocnemius most superficial muscle of the calf
genioglossus muscle that originates on the mandible and allows the tongue to move downward and forward
geniohyoid muscle that depresses the mandible, and raises and pulls the hyoid bone anteriorly
gluteal group muscle group that extends, flexes, rotates, adducts, and abducts the femur
gluteus maximus largest of the gluteus muscles that extends the femur
gluteus medius muscle deep to the gluteus maximus that abducts the femur at the hip
gluteus minimus smallest of the gluteal muscles and deep to the gluteus medius
gracilis muscle that adducts the thigh and flexes the leg at the knee
hamstring group three long muscles on the back of the leg
hyoglossus muscle that originates on the hyoid bone to move the tongue downward and flatten it
hypothenar group of muscles on the medial aspect of the palm
hypothenar eminence rounded contour of muscle at the base of the little finger
iliacus muscle that, along with the psoas major, makes up the iliopsoas
iliococcygeus muscle that makes up the levator ani along with the pubococcygeus
iliocostalis cervicis muscle of the iliocostalis group associated with the cervical region
iliocostalis group laterally placed muscles of the

palmar interossei muscles that abduct and flex each finger at the metacarpophalangeal joints and extend each finger at the interphalangeal joints
palmaris longus muscle that provides weak flexion of the hand at the wrist
parallel fascicles that extend in the same direction as the long axis of the muscle
patellar ligament extension of the quadriceps tendon below the patella
pectineus muscle that abducts and flexes the femur at the hip
pectoral girdle shoulder girdle, made up of the clavicle and scapula
pectoralis major thick, fan-shaped axial muscle that covers much of the superior thorax
pectoralis minor muscle that moves the scapula and assists in inhalation
pelvic diaphragm muscular sheet that comprises the levator ani and the ischiococcygeus
pelvic girdle hips, a foundation for the lower limb
pennate fascicles that are arranged differently based on their angles to the tendon
perineum diamond-shaped region between the pubic symphysis, coccyx, and ischial tuberosities
piriformis muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip
plantar aponeurosis muscle that supports the longitudinal arch of the foot
plantar group four-layered group of intrinsic foot muscles
plantaris muscle that runs obliquely between the gastrocnemius and the soleus
popliteal fossa diamond-shaped space at the back of the knee
popliteus muscle that flexes the leg at the knee and creates the floor of the popliteal fossa
posterior compartment of the leg region that includes the superficial gastrocnemius, soleus, and plantaris, and the deep popliteus, flexor digitorum longus, flexor hallucis longus, and tibialis posterior
posterior compartment of the thigh region that includes muscles that flex the leg and extend the thigh
posterior scalene smallest scalene muscle, located posterior to the middle scalene
prime mover (also, agonist) principle muscle involved in an action
pronator quadratus pronator that originates on the ulna and inserts on the radius
pronator teres pronator that originates on the humerus and inserts on the radius
psoas major muscle that, along with the iliacus, makes up the iliopsoas
pubococcygeus muscle that makes up the levator ani along with the iliococcygeus
quadratus femoris muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip
quadratus lumborum posterior part of the abdominal wall that helps with posture and stabilization of the body
quadriceps femoris group four muscles, that extend and stabilize the knee
quadriceps tendon (also, patellar tendon) tendon common to all four quadriceps muscles, inserts into the patella
rectus straight
rectus abdominis long, linear muscle that extends along the middle of the trunk
rectus femoris quadricep muscle on the anterior aspect of the thigh
rectus sheaths tissue that makes up the linea alba
retinacula fibrous bands that sheath the tendons at the wrist
rhomboid major muscle that attaches the vertebral border of the scapula to the spinous process of the thoracic vertebrae
rhomboid minor muscle that attaches the vertebral border of the scapula to the spinous process of the thoracic vertebrae
rotator cuff (also, musculotendinous cuff) the circle of tendons around the shoulder joint
sartorius band-like muscle that flexes, abducts, and laterally rotates the leg at the hip
scalene muscles flex, laterally flex, and rotate the head; contribute to deep inhalation
segmental muscle group interspinales and intertransversarii muscles that bring together the spinous and transverse processes of each consecutive vertebra
semimembranosus hamstring muscle
semispinalis capitis transversospinales muscle associated with the head region
semispinalis cervicis transversospinales muscle associated with the cervical region
semispinalis thoracis transversospinales muscle associated with the thoracic region
semitendinosus hamstring muscle
serratus anterior large and flat muscle that originates on the ribs and inserts onto the scapula
soleus wide, flat muscle deep to the gastrocnemius
sphincter urethrovaginalis deep perineal muscle in females
spinalis capitis muscle of the spinalis group associated with the head region

called a fixator. Meanwhile, a muscle with the opposite action of the prime mover is called an antagonist. Several factors contribute to the force generated by a skeletal muscle. One is the arrangement of the fascicles in the skeletal muscle. Fascicles can be parallel, circular, convergent, pennate, fusiform, or triangular. Each arrangement has its own range of motion and ability to do work.

11.2 Naming Skeletal Muscles

Muscle names are based on many characteristics. The location of a muscle in the body is important. Some muscles are named based on their size and location, such as the gluteal muscles of the buttocks. Other muscle names can indicate the location in the body or bones with which the muscle is associated, such as the tibialis anterior. The shapes of some muscles are distinctive; for example, the direction of the muscle fibers is used to describe muscles of the body midline. The origin and/or insertion can also be features used to name a muscle; examples are the biceps brachii, triceps brachii, and the pectoralis major.

11.3 Axial Muscles of the Head, Neck, and Back

Muscles are either axial muscles or appendicular. The axial muscles are grouped based on location, function, or both. Some axial muscles cross over to the appendicular skeleton. The muscles of the head and neck are all axial. The muscles in the face create facial expression by inserting into the skin rather than onto bone. Muscles that move the eyeballs are extrinsic, meaning they originate outside of the eye and insert onto it. Tongue muscles are both extrinsic and intrinsic. The genioglossus depresses the tongue and moves it anteriorly; the styloglossus lifts the tongue and retracts it; the palatoglossus elevates the back of the tongue; and the hyoglossus depresses and flattens it. The muscles of the anterior neck facilitate swallowing and speech, stabilize the hyoid bone and position the larynx. The muscles of the neck stabilize and move the head. The sternocleidomastoid divides the neck into anterior and posterior triangles.

The muscles of the back and neck that move the vertebral column are complex, overlapping, and can be divided into five groups. The splenius group includes the splenius capitis and the splenius cervicis. The erector spinae has three subgroups. The iliocostalis group includes the iliocostalis cervicis, the iliocostalis thoracis, and the iliocostalis lumborum. The longissimus group includes the longissimus capitis, the longissimus cervicis, and the longissimus thoracis. The spinalis group includes the spinalis capitis, the spinalis cervicis, and the spinalis thoracis. The transversospinales include the semispinalis capitis, semispinalis cervicis, semispinalis thoracis, multifidus, and rotatores. The segmental muscles include the interspinales and intertransversarii. Finally, the scalenes include the anterior scalene, middle scalene, and posterior scalene.

11.4 Axial Muscles of the Abdominal Wall, and Thorax

Made of skin, fascia, and four pairs of muscle, the anterior abdominal wall protects the organs located in the abdomen and moves the vertebral column. These muscles include the rectus abdominis, which extends through the entire length of the trunk, the external oblique, the internal oblique, and the transversus abdominis. The quadratus lumborum forms the posterior abdominal wall.

The muscles of the thorax play a large role in breathing, especially the dome-shaped diaphragm. When it contracts and flattens, the volume inside the pleural cavities increases, which decreases the pressure within them. As a result, air will flow into the lungs. The external and internal intercostal muscles span the space between the ribs and help change the shape of the rib cage and the volume-pressure ratio inside the pleural cavities during inspiration and expiration.

The perineum muscles play roles in urination in both sexes, ejaculation in males, and vaginal contraction in females. The pelvic floor muscles support the pelvic organs, resist intra-abdominal pressure, and work as sphincters for the urethra, rectum, and vagina.

11.5 Muscles of the Pectoral Girdle and Upper Limbs

The clavicle and scapula make up the pectoral girdle, which provides a stable origin for the muscles that move the humerus. The muscles that position and stabilize the pectoral girdle are located on the thorax. The anterior thoracic muscles are the subclavius, pectoralis minor, and the serratus anterior. The posterior thoracic muscles are the trapezius, levator scapulae, rhomboid major, and rhomboid minor. Nine muscles cross the shoulder joint to move the humerus. The ones that originate on the axial skeleton are the pectoralis major and the latissimus dorsi. The deltoid, subscapularis, supraspinatus, infraspinatus, teres major, teres minor, and coracobrachialis originate on the scapula.

The forearm flexors include the biceps brachii, brachialis, and brachioradialis. The extensors are the

3. Which of the following statements is correct about what happens during flexion?
   a. The angle between bones is increased.
   b. The angle between bones is decreased.
   c. The bone moves away from the body.
   d. The bone moves toward the center of the body.

4. Which is moved the *least* during muscle contraction?
   a. the origin
   b. the insertion
   c. the ligaments
   d. the joints

5. Which muscle has a convergent pattern of fascicles?
   a. biceps brachii
   b. gluteus maximus
   c. pectoralis major
   d. rectus femoris

6. A muscle that has a pattern of fascicles running along the long axis of the muscle has which of the following fascicle arrangements?
   a. circular
   b. pennate
   c. parallel
   d. rectus

7. Which arrangement *best* describes a bipennate muscle?
   a. The muscle fibers feed in on an angle to a long tendon from both sides.
   b. The muscle fibers feed in on an angle to a long tendon from all directions.
   c. The muscle fibers feed in on an angle to a long tendon from one side.
   d. The muscle fibers on one side of a tendon feed into it at a certain angle and muscle fibers on the other side of the tendon feed into it at the opposite angle.

8. The location of a muscle's insertion and origin can determine _____.
   a. action
   b. the force of contraction
   c. muscle name
   d. the load a muscle can carry

9. Where is the temporalis muscle located?
   a. on the forehead
   b. in the neck
   c. on the side of the head
   d. on the chin

10. Which muscle name does *not* make sense?
   a. extensor digitorum
   b. gluteus minimus
   c. biceps femoris
   d. extensor minimus longus

11. Which of the following terms would be used in the name of a muscle that moves the leg away from the body?
   a. flexor
   b. adductor
   c. extensor
   d. abductor

12. Which of the following is a prime mover in head flexion?
   a. occipitofrontalis
   b. corrugator supercilii
   c. sternocleidomastoid
   d. masseter

13. Where is the inferior oblique muscle located?
   a. in the abdomen
   b. in the eye socket
   c. in the anterior neck
   d. in the face

14. What is the action of the masseter?
   a. swallowing
   b. chewing
   c. moving the lips
   d. closing the eye

15. The names of the extrinsic tongue muscles commonly end in _____.
   a. -glottis
   b. -glossus
   c. -gluteus
   d. -hyoid

16. What is the function of the erector spinae?
   a. movement of the arms
   b. stabilization of the pelvic girdle
   c. postural support
   d. rotating of the vertebral column

17. Which of the following abdominal muscles is not a part of the anterior abdominal wall?
   a. quadratus lumborum
   b. rectus abdominis
   c. interior oblique
   d. exterior oblique

12.1 Basic Structure and Function of the Nervous System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the anatomical and functional divisions of the nervous system
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons
- List the basic functions of the nervous system

The picture you have in your mind of the nervous system probably includes the **brain**, the nervous tissue contained within the cranium, and the **spinal cord**, the extension of nervous tissue within the vertebral column. That suggests it is made of two organs—and you may not even think of the spinal cord as an organ—but the nervous system is a very complex structure. Within the brain, many different and separate regions are responsible for many different and separate functions. It is as if the nervous system is composed of many organs that all look similar and can only be differentiated using tools such as the microscope or electrophysiology. In comparison, it is easy to see that the stomach is different than the esophagus or the liver, so you can imagine the digestive system as a collection of specific organs.

The Central and Peripheral Nervous Systems

The nervous system can be divided into two major regions: the central and peripheral nervous systems. The **central nervous system (CNS)** is the brain and spinal cord, and the **peripheral nervous system (PNS)** is everything else (Figure 12.2). The brain is contained within the cranial cavity of the skull, and the spinal cord is contained within the vertebral cavity of the vertebral column. It is a bit of an oversimplification to say that the CNS is what is inside these two cavities and the peripheral nervous system is outside of them, but that is one way to start to think about it. In actuality, there are some elements of the peripheral nervous system that are within the cranial or vertebral cavities. The peripheral nervous system is so named because it is on the periphery—meaning beyond the brain and spinal cord. Depending on different aspects of the nervous system, the dividing line between central and peripheral is not necessarily universal.

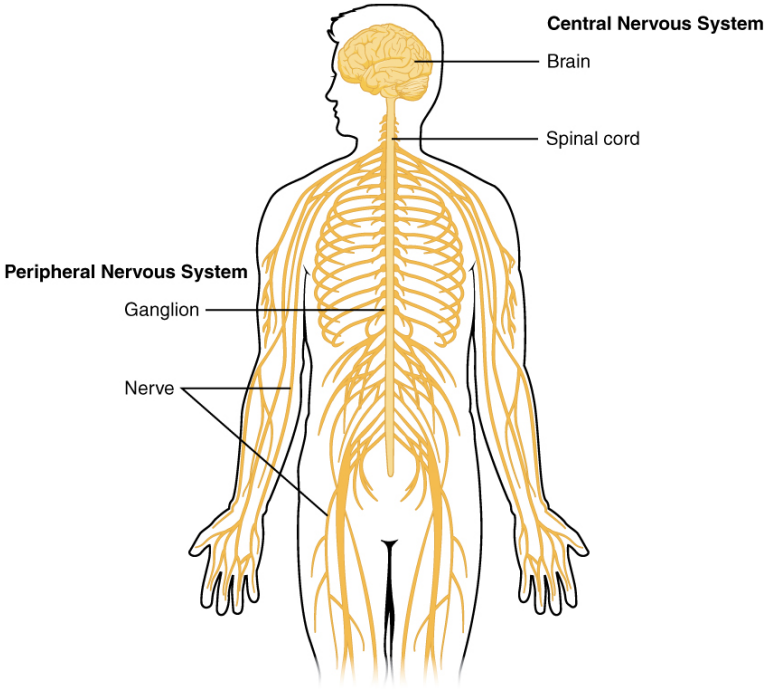


FIGURE 12.2 Central and Peripheral Nervous System The structures of the PNS are referred to as ganglia and nerves, which can be seen as distinct structures. The equivalent structures in the CNS are not obvious from this overall perspective and are best examined in prepared tissue under the microscope.

Nervous tissue, present in both the CNS and PNS, contains two basic types of cells: neurons and glial cells. A **glial cell** is one of a variety of cells that provide a framework of tissue that supports the neurons and their activities. The

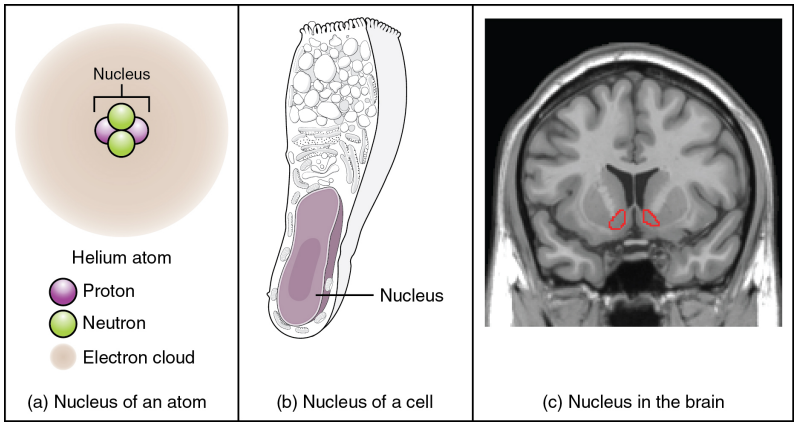


FIGURE 12.4 What Is a Nucleus? (a) The nucleus of an atom contains its protons and neutrons. (b) The nucleus of a cell is the organelle that contains DNA. (c) A nucleus in the CNS is a localized center of function with the cell bodies of several neurons, shown here circled in red. (credit c: "Was a bee"/Wikimedia Commons)

Terminology applied to bundles of axons also differs depending on location. A bundle of axons, or fibers, found in the CNS is called a **tract** whereas the same thing in the PNS would be called a **nerve**. There is an important point to make about these terms, which is that they can both be used to refer to the same bundle of axons. When those axons are in the PNS, the term is nerve, but if they are CNS, the term is tract. The most obvious example of this is the axons that project from the retina into the brain. Those axons are called the optic nerve as they leave the eye, but when they are inside the cranium, they are referred to as the optic tract. There is a specific place where the name changes, which is the optic chiasm, but they are still the same axons (Figure 12.5). A similar situation outside of science can be described for some roads. Imagine a road called "Broad Street" in a town called "Anyville." The road leaves Anyville and goes to the next town over, called "Hometown." When the road crosses the line between the two towns and is in Hometown, its name changes to "Main Street." That is the idea behind the naming of the retinal axons. In the PNS, they are called the optic nerve, and in the CNS, they are the optic tract. Table 12.1 helps to clarify which of these terms apply to the central or peripheral nervous systems.

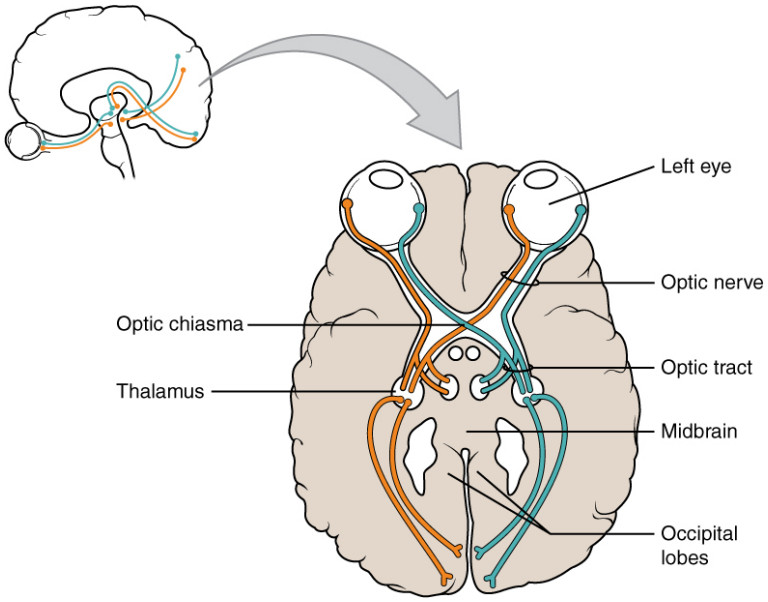


FIGURE 12.5 Optic Nerve Versus Optic Tract This drawing of the connections of the eye to the brain shows the optic nerve extending from the eye to the chiasm, where the structure continues as the optic tract. The same axons extend from the eye to the brain through these two bundles of fibers, but the chiasm represents the border between peripheral and central.

INTERACTIVE LINK

In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique

broader uses of the term. The nervous system can cause the contraction of all three types of muscle tissue. For example, skeletal muscle contracts to move the skeleton, cardiac muscle is influenced as heart rate increases during exercise, and smooth muscle contracts as the digestive system moves food along the digestive tract. Responses also include the neural control of glands in the body as well, such as the production and secretion of sweat by the eccrine and merocrine sweat glands found in the skin to lower body temperature.

Responses can be divided into those that are voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands). Voluntary responses are governed by the somatic nervous system and involuntary responses are governed by the autonomic nervous system, which are discussed in the next section.

Integration. Stimuli that are received by sensory structures are communicated to the nervous system where that information is processed. This is called integration. Stimuli are compared with, or integrated with, other stimuli, memories of previous stimuli, or the state of a person at a particular time. This leads to the specific response that will be generated. Seeing a baseball pitched to a batter will not automatically cause the batter to swing. The trajectory of the ball and its speed will need to be considered. Maybe the count is three balls and one strike, and the batter wants to let this pitch go by in the hope of getting a walk to first base. Or maybe the batter's team is so far ahead, it would be fun to just swing away.

Controlling the Body

The nervous system can be divided into two parts mostly on the basis of a functional difference in responses. The **somatic nervous system (SNS)** is responsible for conscious perception and voluntary motor responses. Voluntary motor response means the contraction of skeletal muscle, but those contractions are not always voluntary in the sense that you have to want to perform them. Some somatic motor responses are reflexes, and often happen without a conscious decision to perform them. If your friend jumps out from behind a corner and yells "Boo!" you will be startled and you might scream or leap back. You didn't decide to do that, and you may not have wanted to give your friend a reason to laugh at your expense, but it is a reflex involving skeletal muscle contractions. Other motor responses become automatic (in other words, unconscious) as a person learns motor skills (referred to as "habit learning" or "procedural memory").

The **autonomic nervous system (ANS)** is responsible for involuntary control of the body, usually for the sake of homeostasis (regulation of the internal environment). Sensory input for autonomic functions can be from sensory structures tuned to external or internal environmental stimuli. The motor output extends to smooth and cardiac muscle as well as glandular tissue. The role of the autonomic system is to regulate the organ systems of the body, which usually means to control homeostasis. Sweat glands, for example, are controlled by the autonomic system. When you are hot, sweating helps cool your body down. That is a homeostatic mechanism. But when you are nervous, you might start sweating also. That is not homeostatic, it is the physiological response to an emotional state.

There is another division of the nervous system that describes functional responses. The **enteric nervous system (ENS)** is responsible for controlling the smooth muscle and glandular tissue in your digestive system. It is a large part of the PNS, and is not dependent on the CNS. It is sometimes valid, however, to consider the enteric system to be a part of the autonomic system because the neural structures that make up the enteric system are a component of the autonomic output that regulates digestion. There are some differences between the two, but for our purposes here there will be a good bit of overlap. See Figure 12.6 for examples of where these divisions of the nervous system can be found.

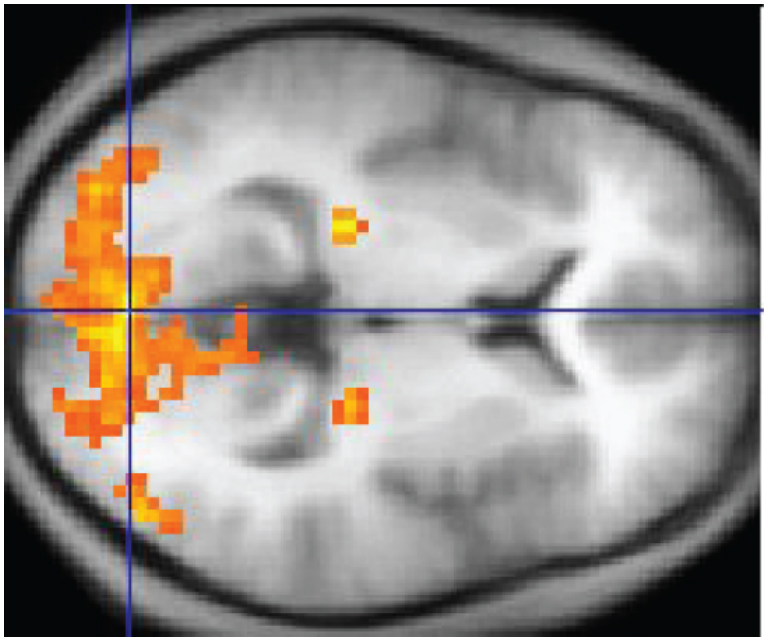


FIGURE 12.7 fMRI This fMRI shows activation of the visual cortex in response to visual stimuli. (credit: "Superborsuk"/Wikimedia Commons)

The underlying assumption is that active nervous tissue will have greater blood flow. By having the subject perform a visual task, activity all over the brain can be measured. Consider this possible experiment: the subject is told to look at a screen with a black dot in the middle (a fixation point). A photograph of a face is projected on the screen away from the center. The subject has to look at the photograph and decipher what it is. The subject has been instructed to push a button if the photograph is of someone they recognize. The photograph might be of a celebrity, so the subject would press the button, or it might be of a random person unknown to the subject, so the subject would not press the button.

In this task, visual sensory areas would be active, integrating areas would be active, motor areas responsible for moving the eyes would be active, and motor areas for pressing the button with a finger would be active. Those areas are distributed all around the brain and the fMRI images would show activity in more than just 10 percent of the brain (some evidence suggests that about 80 percent of the brain is using energy—based on blood flow to the tissue—during well-defined tasks similar to the one suggested above). This task does not even include all of the functions the brain performs. There is no language response, the body is mostly lying still in the MRI machine, and it does not consider the autonomic functions that would be ongoing in the background.

12.2 Nervous Tissue

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the basic structure of a neuron
- Identify the different types of neurons on the basis of polarity
- List the glial cells of the CNS and describe their function
- List the glial cells of the PNS and describe their function

Nervous tissue is composed of two types of cells, neurons and glial cells. Neurons are the primary type of cell that most anyone associates with the nervous system. They are responsible for the computation and communication that the nervous system provides. They are electrically active and release chemical signals to target cells. Glial cells, or glia, are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

the rest are dendrites. Because information flows through the neuron from dendrites or cell bodies toward the axon, these names are based on the neuron's polarity (Figure 12.9).

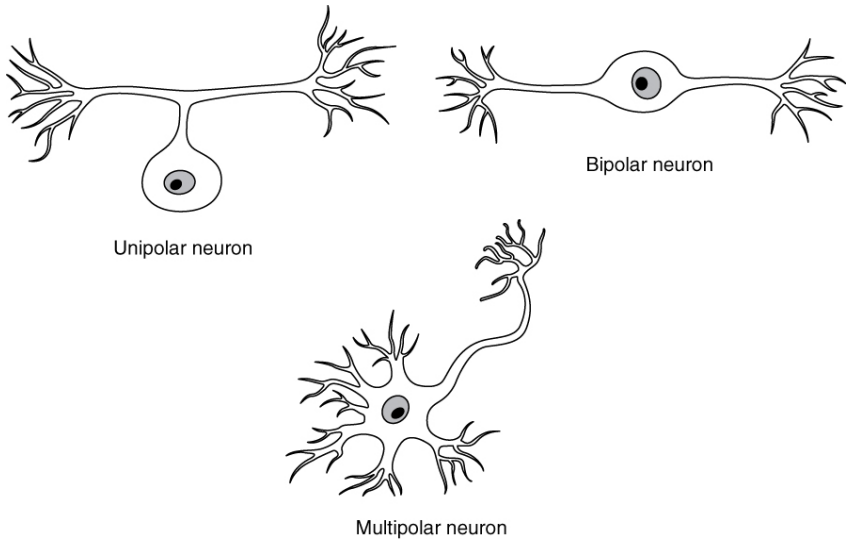


FIGURE 12.9 **Neuron Classification by Shape** Unipolar cells have one process that includes both the axon and dendrite. Bipolar cells have two processes, the axon and a dendrite. Multipolar cells have more than two processes, the axon and two or more dendrites.

Unipolar cells have only one process emerging from the cell. True unipolar cells are only found in invertebrate animals, so the unipolar cells in humans are more appropriately called "pseudo-unipolar" cells. Invertebrate unipolar cells do not have dendrites. Human unipolar cells have an axon that emerges from the cell body, but it splits so that the axon can extend along a very long distance. At one end of the axon are dendrites, and at the other end, the axon forms synaptic connections with a target. Unipolar cells are exclusively sensory neurons and have two unique characteristics. First, their dendrites are receiving sensory information, sometimes directly from the stimulus itself. Secondly, the cell bodies of unipolar neurons are always found in ganglia. Sensory reception is a peripheral function (those dendrites are in the periphery, perhaps in the skin) so the cell body is in the periphery, though closer to the CNS in a ganglion. The axon projects from the dendrite endings, past the cell body in a ganglion, and into the central nervous system.

Bipolar cells have two processes, which extend from each end of the cell body, opposite to each other. One is the axon and one the dendrite. Bipolar cells are not very common. They are found mainly in the olfactory epithelium (where smell stimuli are sensed), and as part of the retina.

Multipolar neurons are all of the neurons that are not unipolar or bipolar. They have one axon and two or more dendrites (usually many more). With the exception of the unipolar sensory ganglion cells, and the two specific bipolar cells mentioned above, all other neurons are multipolar. Some cutting edge research suggests that certain neurons in the CNS do not conform to the standard model of "one, and only one" axon. Some sources describe a fourth type of neuron, called an anaxonic neuron. The name suggests that it has no axon (an- = "without"), but this is not accurate. Anaxonic neurons are very small, and if you look through a microscope at the standard resolution used in histology (approximately 400X to 1000X total magnification), you will not be able to distinguish any process specifically as an axon or a dendrite. Any of those processes can function as an axon depending on the conditions at any given time. Nevertheless, even if they cannot be easily seen, and one specific process is definitively the axon, these neurons have multiple processes and are therefore multipolar.

Neurons can also be classified on the basis of where they are found, who found them, what they do, or even what chemicals they use to communicate with each other. Some neurons referred to in this section on the nervous system are named on the basis of those sorts of classifications (Figure 12.10). For example, a multipolar neuron that has a very important role to play in a part of the brain called the cerebellum is known as a Purkinje (commonly pronounced per-KIN-gee) cell. It is named after the anatomist who discovered it (Jan Evangelista Purkinje, 1787–1869).

excess signaling molecules, reacting to tissue damage, and contributing to the **blood-brain barrier (BBB)**. The blood-brain barrier is a physiological barrier that keeps many substances that circulate in the rest of the body from getting into the central nervous system, restricting what can cross from circulating blood into the CNS. Nutrient molecules, such as glucose or amino acids, can pass through the BBB, but other molecules cannot. This actually causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the BBB as well as have an effect on the nervous system.

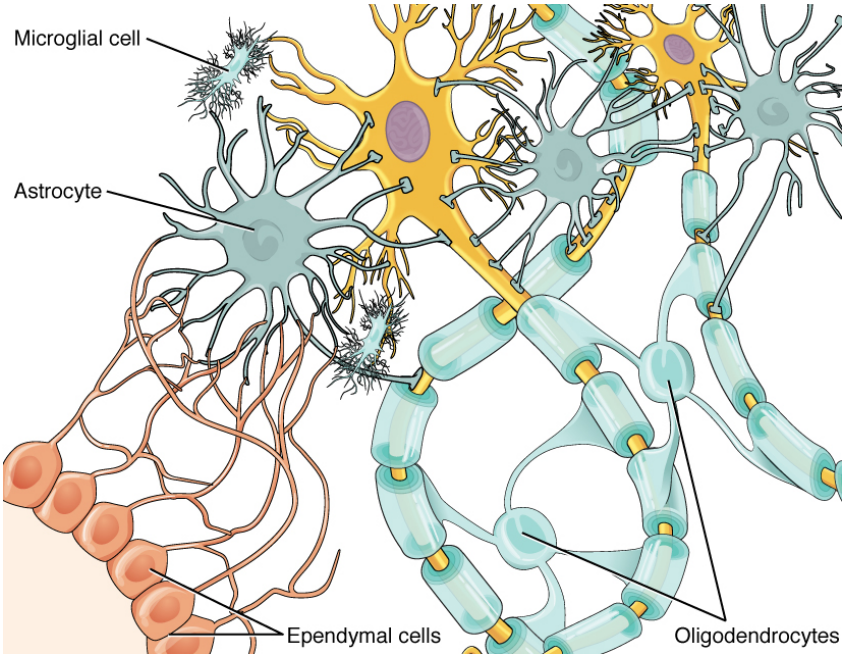


FIGURE 12.11 Glial Cells of the CNS The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.

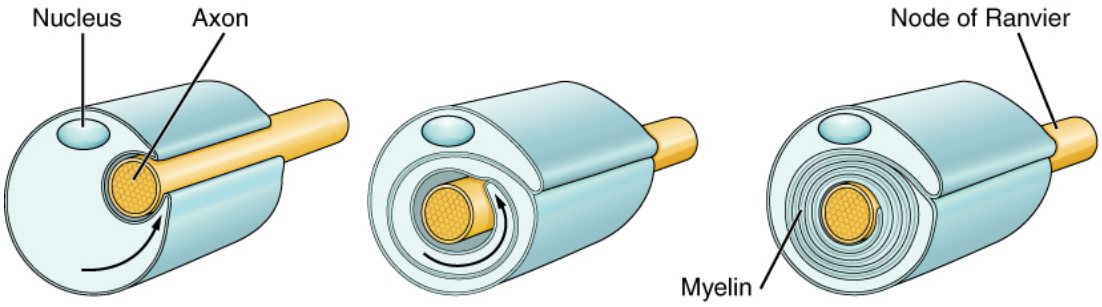
Like a few other parts of the body, the brain has a privileged blood supply. Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. Because of this, only specific types of molecules can enter the CNS. Glucose—the primary energy source—is allowed, as are amino acids. Water and some other small particles, like gases and ions, can enter. But most everything else cannot, including white blood cells, which are one of the body's main lines of defense. While this barrier protects the CNS from exposure to toxic or pathogenic substances, it also keeps out the cells that could protect the brain and spinal cord from disease and damage. The BBB also makes it harder for pharmaceuticals to be developed that can affect the nervous system. Aside from finding efficacious substances, the means of delivery is also crucial.

Also found in CNS tissue is the **oligodendrocyte**, sometimes called just "oligo," which is the glial cell type that insulates axons in the CNS. The name means "cell of a few branches" (oligo- = "few"; dendro- = "branches"; -cyte = "cell"). There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte will provide the myelin for multiple axon segments, either for the same axon or for separate axons. The function of myelin will be discussed below.

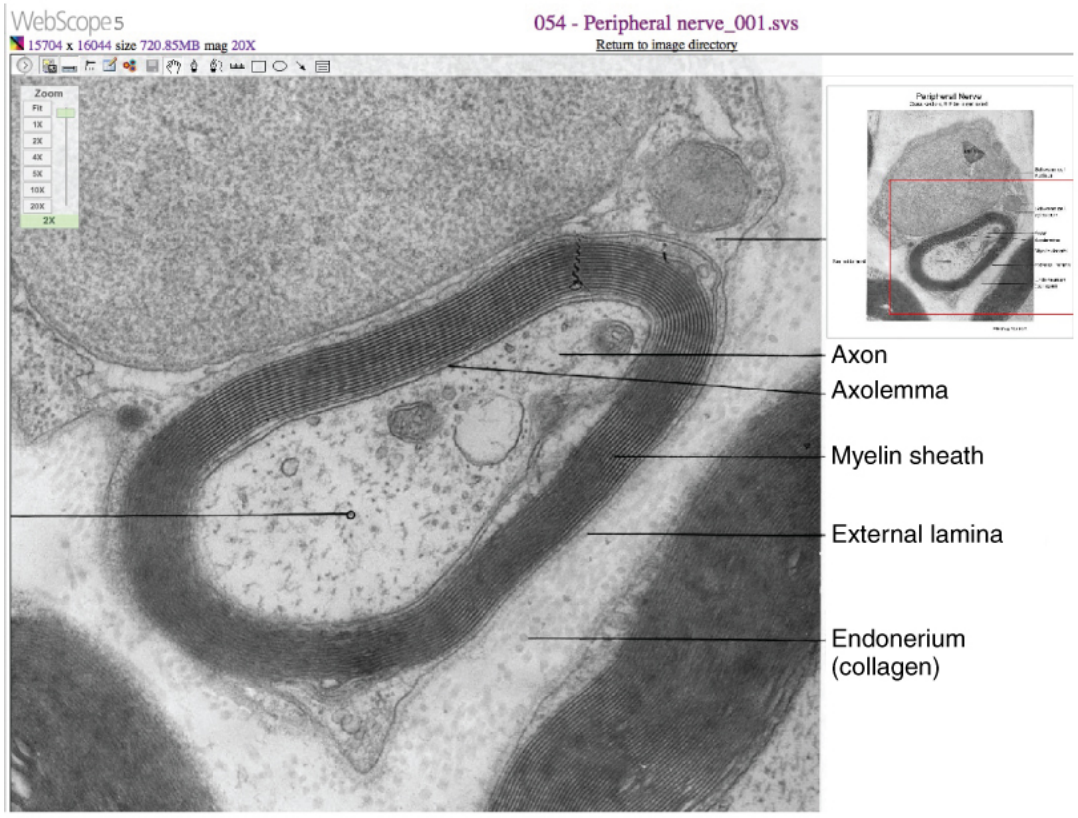
Microglia are, as the name implies, smaller than most of the other glial cells. Ongoing research into these cells, although not entirely conclusive, suggests that they may originate as white blood cells, called macrophages, that become part of the CNS during early development. While their origin is not conclusively determined, their function is related to what macrophages do in the rest of the body. When macrophages encounter diseased or damaged cells in the rest of the body, they ingest and digest those cells or the pathogens that cause disease. Microglia are the cells in the CNS that can do this in normal, healthy tissue, and they are therefore also referred to as CNS-resident macrophages.

The **ependymal cell** is a glial cell that filters blood to make **cerebrospinal fluid (CSF)**, the fluid that circulates through the CNS. Because of the privileged blood supply inherent in the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood. Ependymal cells line each **ventricle**, one of four central

Myelin sheaths can extend for one or two millimeters, depending on the diameter of the axon. Axon diameters can be as small as 1 to 20 micrometers. Because a micrometer is 1/1000 of a millimeter, this means that the length of a myelin sheath can be 100–1000 times the diameter of the axon. Figure 12.8, Figure 12.11, and Figure 12.12 show the myelin sheath surrounding an axon segment, but are not to scale. If the myelin sheath were drawn to scale, the neuron would have to be immense—possibly covering an entire wall of the room in which you are sitting.



(a)



(b)

FIGURE 12.13 **The Process of Myelination** Myelinating glia wrap several layers of cell membrane around the cell membrane of an axon segment. A single Schwann cell insulates a segment of a peripheral nerve, whereas in the CNS, an oligodendrocyte may provide insulation for a few separate axon segments. EM × 1,460,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Disorders of the...

Nervous Tissue

Several diseases can result from the demyelination of axons. The causes of these diseases are not the same; some have genetic causes, some are caused by pathogens, and others are the result of autoimmune disorders. Though the causes are varied, the results are largely similar. The myelin insulation of axons is compromised,

Imagine you are about to take a shower in the morning before going to school. You have turned on the faucet to start the water as you prepare to get in the shower. After a few minutes, you expect the water to be a temperature that will be comfortable to enter. So you put your hand out into the spray of water. What happens next depends on how your nervous system interacts with the stimulus of the water temperature and what you do in response to that stimulus.

Found in the skin of your fingers or toes is a type of sensory receptor that is sensitive to temperature, called a **thermoreceptor**. When you place your hand under the shower (Figure 12.15), the cell membrane of the thermoreceptors changes its electrical state (voltage). The amount of change is dependent on the strength of the stimulus (how hot the water is). This is called a **graded potential**. If the stimulus is strong, the voltage of the cell membrane will change enough to generate an electrical signal that will travel down the axon. You have learned about this type of signaling before, with respect to the interaction of nerves and muscles at the neuromuscular junction. The voltage at which such a signal is generated is called the **threshold**, and the resulting electrical signal is called an **action potential**. In this example, the action potential travels—a process known as **propagation**—along the axon from the axon hillock to the axon terminals and into the synaptic end bulbs. When this signal reaches the end bulbs, it causes the release of a signaling molecule called a **neurotransmitter**.

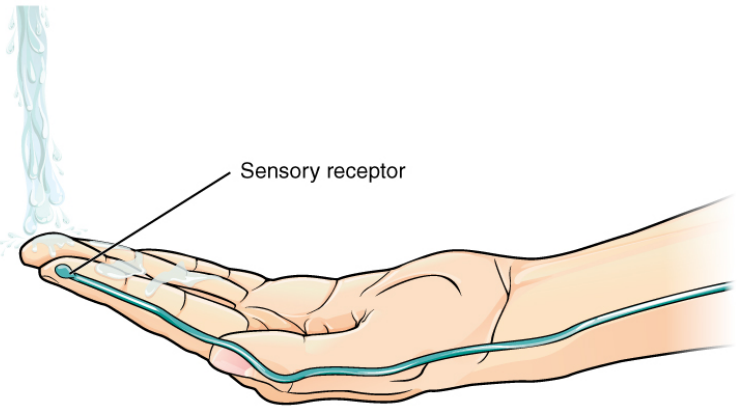


FIGURE 12.15 The Sensory Input Receptors in the skin sense the temperature of the water.

The neurotransmitter diffuses across the short distance of the synapse and binds to a receptor protein of the target neuron. When the molecular signal binds to the receptor, the cell membrane of the target neuron changes its electrical state and a new graded potential begins. If that graded potential is strong enough to reach threshold, the second neuron generates an action potential at its axon hillock. The target of this neuron is another neuron in the **thalamus** of the brain, the part of the CNS that acts as a relay for sensory information. At another synapse, neurotransmitter is released and binds to its receptor. The thalamus then sends the sensory information to the **cerebral cortex**, the outermost layer of gray matter in the brain, where conscious perception of that water temperature begins.

Within the cerebral cortex, information is processed among many neurons, integrating the stimulus of the water temperature with other sensory stimuli, with your emotional state (you just aren't ready to wake up; the bed is calling to you), memories (perhaps of the lab notes you have to study before a quiz). Finally, a plan is developed about what to do, whether that is to turn the temperature up, turn the whole shower off and go back to bed, or step into the shower. To do any of these things, the cerebral cortex has to send a command out to your body to move muscles (Figure 12.16).

Others with a medical degree and a specialization in neuroscience go on to work directly with patients, diagnosing and treating mental disorders. You can do this as a psychiatrist, a neuropsychologist, a neuroscience nurse, or a neurodiagnostic technician, among other possible career paths.

12.4 The Action Potential

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential

The functions of the nervous system—sensation, integration, and response—depend on the functions of the neurons underlying these pathways. To understand how neurons are able to communicate, it is necessary to describe the role of an **excitable membrane** in generating these signals. The basis of this communication is the action potential, which demonstrates how changes in the membrane can constitute a signal. Looking at the way these signals work in more variable circumstances involves a look at graded potentials, which will be covered in the next section.

Electrically Active Cell Membranes

Most cells in the body make use of charged particles, ions, to build up a charge across the cell membrane. Previously, this was shown to be a part of how muscle cells work. For skeletal muscles to contract, based on excitation–contraction coupling, requires input from a neuron. Both of the cells make use of the cell membrane to regulate ion movement between the extracellular fluid and cytosol.

As you learned in the chapter on cells, the cell membrane is primarily responsible for regulating what can cross the membrane and what stays on only one side. The cell membrane is a phospholipid bilayer, so only substances that can pass directly through the hydrophobic core can diffuse through unaided. Charged particles, which are hydrophilic by definition, cannot pass through the cell membrane without assistance (Figure 12.17). Transmembrane proteins, specifically channel proteins, make this possible. Several passive transport channels, as well as active transport pumps, are necessary to generate a transmembrane potential and an action potential. Of special interest is the carrier protein referred to as the sodium/potassium pump that moves sodium ions (Na^+) out of a cell and potassium ions (K^+) into a cell, thus regulating ion concentration on both sides of the cell membrane.

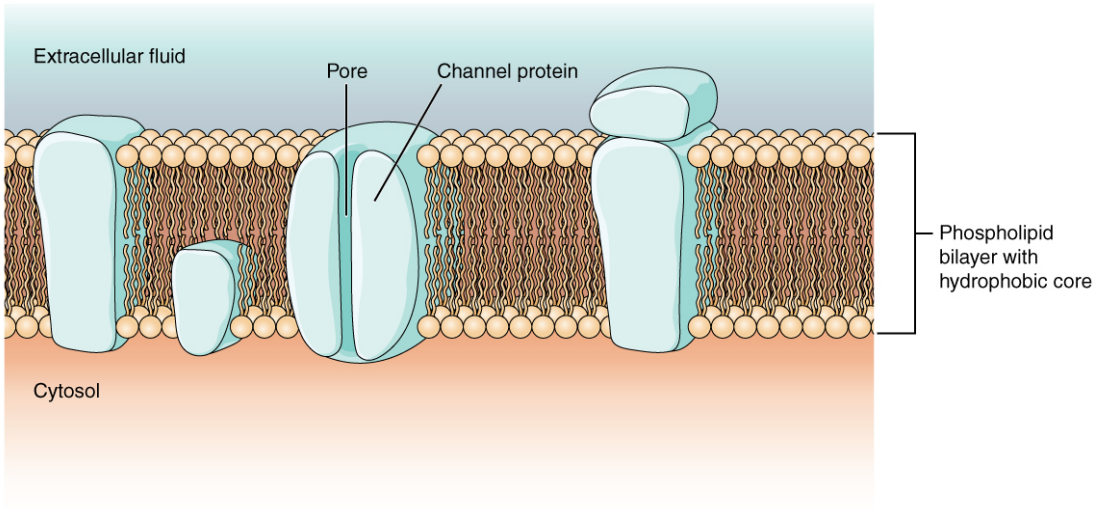


FIGURE 12.17 Cell Membrane and Transmembrane Proteins The cell membrane is composed of a phospholipid bilayer and has many transmembrane proteins, including different types of channel proteins that serve as ion channels.

The sodium/potassium pump requires energy in the form of adenosine triphosphate (ATP), so it is also referred to as an ATPase. As was explained in the cell chapter, the concentration of Na^+ is higher outside the cell than inside, and the concentration of K^+ is higher inside the cell than outside. That means that this pump is moving the ions against the concentration gradients for sodium and potassium, which is why it requires energy. In fact, the pump basically maintains those concentration gradients.

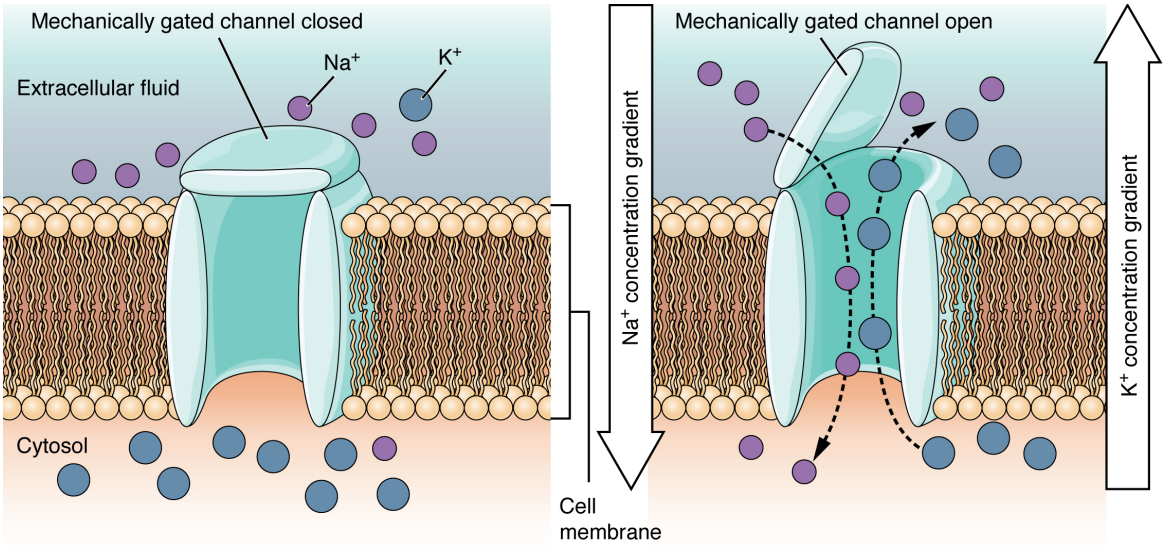


FIGURE 12.19 Mechanically Gated Channels When a mechanical change occurs in the surrounding tissue, such as pressure or touch, the channel is physically opened. Thermoreceptors work on a similar principle. When the local tissue temperature changes, the protein reacts by physically opening the channel.

A **voltage-gated channel** is a channel that responds to changes in the electrical properties of the membrane in which it is embedded. Normally, the inner portion of the membrane is at a negative voltage. When that voltage becomes less negative, the channel begins to allow ions to cross the membrane (Figure 12.20).

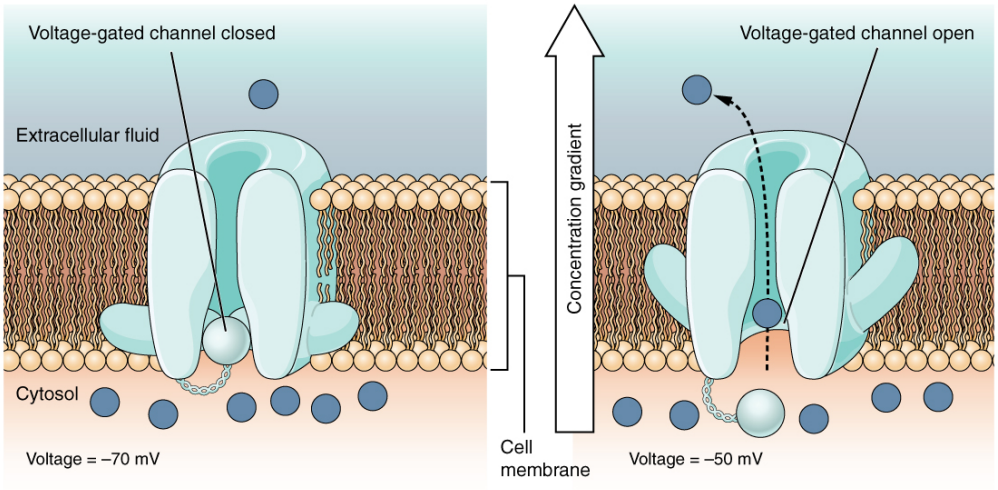


FIGURE 12.20 Voltage-Gated Channels Voltage-gated channels open when the transmembrane voltage changes around them. Amino acids in the structure of the protein are sensitive to charge and cause the pore to open to the selected ion.

A **leakage channel** is randomly gated, meaning that it opens and closes at random, hence the reference to leaking. There is no actual event that opens the channel; instead, it has an intrinsic rate of switching between the open and closed states. Leakage channels contribute to the resting transmembrane voltage of the excitable membrane (Figure 12.21).

Large anions are a component of the inner cell membrane, including specialized phospholipids and proteins associated with the inner leaflet of the membrane (leaflet is a term used for one side of the lipid bilayer membrane). The negative charge is localized in the large anions.

With the ions distributed across the membrane at these concentrations, the difference in charge is measured at -70 mV, the value described as the **resting membrane potential**. The exact value measured for the resting membrane potential varies between cells, but -70 mV is most commonly used as this value. This voltage would actually be much lower except for the contributions of some important proteins in the membrane. Leakage channels allow Na^+ to slowly move into the cell or K^+ to slowly move out, and the Na^+/K^+ pump restores them. This may appear to be a waste of energy, but each has a role in maintaining the membrane potential.

The Action Potential

Resting membrane potential describes the steady state of the cell, which is a dynamic process that is balanced by ion leakage and ion pumping. Without any outside influence, it will not change. To get an electrical signal started, the membrane potential has to change.

This starts with a channel opening for Na^+ in the membrane. Because the concentration of Na^+ is higher outside the cell than inside the cell by a factor of 10, ions will rush into the cell that are driven largely by the concentration gradient. Because sodium is a positively charged ion, it will change the relative voltage immediately inside the cell relative to immediately outside. The resting potential is the state of the membrane at a voltage of -70 mV, so the sodium cation entering the cell will cause it to become less negative. This is known as **depolarization**, meaning the membrane potential moves toward zero.

The concentration gradient for Na^+ is so strong that it will continue to enter the cell even after the membrane potential has become zero, so that the voltage immediately around the pore begins to become positive. The electrical gradient also plays a role, as negative proteins below the membrane attract the sodium ion. The membrane potential will reach +30 mV by the time sodium has entered the cell.

As the membrane potential reaches +30 mV, other voltage-gated channels are opening in the membrane. These channels are specific for the potassium ion. A concentration gradient acts on K^+, as well. As K^+ starts to leave the cell, taking a positive charge with it, the membrane potential begins to move back toward its resting voltage. This is called **repolarization**, meaning that the membrane voltage moves back toward the -70 mV value of the resting membrane potential.

Repolarization returns the membrane potential to the -70 mV value that indicates the resting potential, but it actually overshoots that value. Potassium ions reach equilibrium when the membrane voltage is below -70 mV, so a period of hyperpolarization occurs while the K^+ channels are open. Those K^+ channels are slightly delayed in closing, accounting for this short overshoot.

What has been described here is the action potential, which is presented as a graph of voltage over time in Figure 12.23. It is the electrical signal that nervous tissue generates for communication. The change in the membrane voltage from -70 mV at rest to +30 mV at the end of depolarization is a 100 mV change. That can also be written as a 0.1 V change. To put that value in perspective, think about a battery. An AA battery that you might find in a television remote has a voltage of 1.5 V, or a 9 V battery (the rectangular battery with two posts on one end) is, obviously, 9 V. The change seen in the action potential is one or two orders of magnitude less than the charge in these batteries. In fact, the membrane potential can be described as a battery. A charge is stored across the membrane that can be released under the correct conditions. A battery in your remote has stored a charge that is “released” when you push a button.

has two gates. One is the **activation gate**, which opens when the membrane potential crosses -55 mV. The other gate is the **inactivation gate**, which closes after a specific period of time—on the order of a fraction of a millisecond. When a cell is at rest, the activation gate is closed and the inactivation gate is open. However, when the threshold is reached, the activation gate opens, allowing Na^+ to rush into the cell. Timed with the peak of depolarization, the inactivation gate closes. During repolarization, no more sodium can enter the cell. When the membrane potential passes -55 mV again, the activation gate closes. After that, the inactivation gate re-opens, making the channel ready to start the whole process over again.

The voltage-gated K^+ channel has only one gate, which is sensitive to a membrane voltage of -50 mV. However, it does not open as quickly as the voltage-gated Na^+ channel does. It might take a fraction of a millisecond for the channel to open once that voltage has been reached. The timing of this coincides exactly with when the Na^+ flow peaks, so voltage-gated K^+ channels open just as the voltage-gated Na^+ channels are being inactivated. As the membrane potential repolarizes and the voltage passes -50 mV again, the channel closes—again, with a little delay. Potassium continues to leave the cell for a short while and the membrane potential becomes more negative, resulting in the hyperpolarizing overshoot. Then the channel closes again and the membrane can return to the resting potential because of the ongoing activity of the non-gated channels and the Na^+/K^+ pump.

All of this takes place within approximately 2 milliseconds (Figure 12.24). While an action potential is in progress, another one cannot be initiated. That effect is referred to as the **refractory period**. There are two phases of the refractory period: the **absolute refractory period** and the **relative refractory period**. During the absolute phase, another action potential will not start. This is because of the inactivation gate of the voltage-gated Na^+ channel. Once that channel is back to its resting conformation (less than -55 mV), a new action potential could be started, but only by a stronger stimulus than the one that initiated the current action potential. This is because of the flow of K^+ out of the cell. Because that ion is rushing out, any Na^+ that tries to enter will not depolarize the cell, but will only keep the cell from hyperpolarizing.

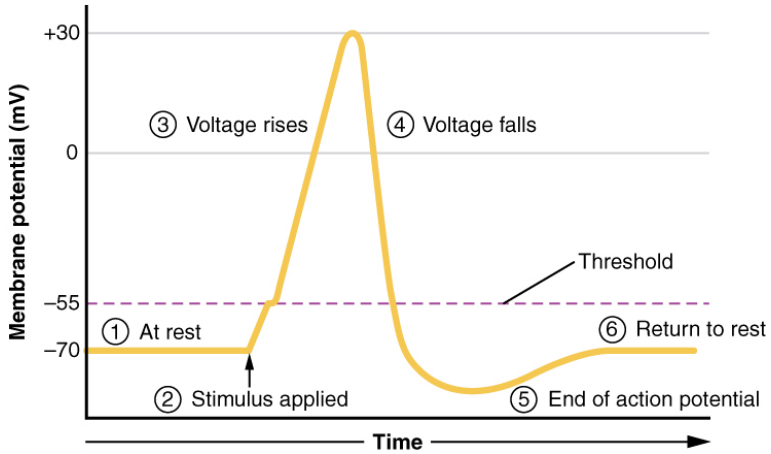


FIGURE 12.24 Stages of an Action Potential Plotting voltage measured across the cell membrane against time, the events of the action potential can be related to specific changes in the membrane voltage. (1) At rest, the membrane voltage is -70 mV. (2) The membrane begins to depolarize when an external stimulus is applied. (3) The membrane voltage begins a rapid rise toward +30 mV. (4) The membrane voltage starts to return to a negative value. (5) Repolarization continues past the resting membrane voltage, resulting in hyperpolarization. (6) The membrane voltage returns to the resting value shortly after hyperpolarization.

Propagation of the Action Potential

The action potential is initiated at the beginning of the axon, at what is called the initial segment. There is a high density of voltage-gated Na^+ channels so that rapid depolarization can take place here. Going down the length of the axon, the action potential is propagated because more voltage-gated Na^+ channels are opened as the depolarization spreads. This spreading occurs because Na^+ enters through the channel and moves along the inside of the cell membrane. As the Na^+ moves, or flows, a short distance along the cell membrane, its positive charge depolarizes a little more of the cell membrane. As that depolarization spreads, new voltage-gated Na^+ channels open and more ions rush into the cell, spreading the depolarization a little farther.

Because voltage-gated Na^+ channels are inactivated at the peak of the depolarization, they cannot be opened again for a brief time—the absolute refractory period. Because of this, depolarization spreading back toward previously opened channels has no effect. The action potential must propagate toward the axon terminals; as a result, the

12.5 Communication Between Neurons

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the differences between the types of graded potentials
- Categorize the major neurotransmitters by chemical type and effect

The electrical changes taking place within a neuron, as described in the previous section, are similar to a light switch being turned on. A stimulus starts the depolarization, but the action potential runs on its own once a threshold has been reached. The question is now, "What flips the light switch on?" Temporary changes to the cell membrane voltage can result from neurons receiving information from the environment, or from the action of one neuron on another. These special types of potentials influence a neuron and determine whether an action potential will occur or not. Many of these transient signals originate at the synapse.

Graded Potentials

Local changes in the membrane potential are called graded potentials and are usually associated with the dendrites of a neuron. The amount of change in the membrane potential is determined by the size of the stimulus that causes it. In the example of testing the temperature of the shower, slightly warm water would only initiate a small change in a thermoreceptor, whereas hot water would cause a large amount of change in the membrane potential.

Graded potentials can be of two sorts, either they are depolarizing or hyperpolarizing (Figure 12.25). For a membrane at the resting potential, a graded potential represents a change in that voltage either above -70 mV or below -70 mV. Depolarizing graded potentials are often the result of Na^+ or Ca^{2+} entering the cell. Both of these ions have higher concentrations outside the cell than inside; because they have a positive charge, they will move into the cell causing it to become less negative relative to the outside. Hyperpolarizing graded potentials can be caused by K^+ leaving the cell or Cl^- entering the cell. If a positive charge moves out of a cell, the cell becomes more negative; if a negative charge enters the cell, the same thing happens.

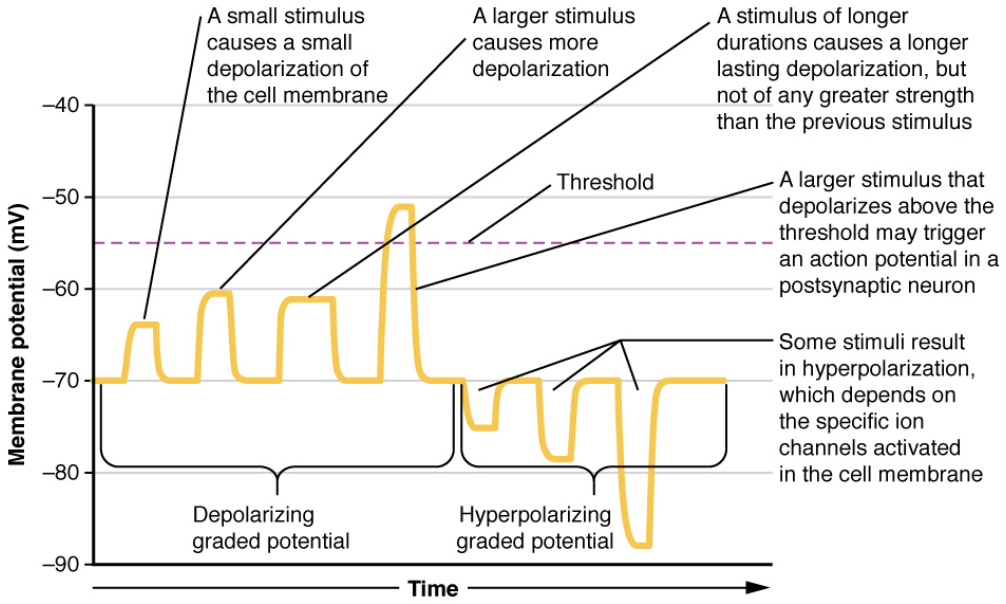


FIGURE 12.25 Graded Potentials Graded potentials are temporary changes in the membrane voltage, the characteristics of which depend on the size of the stimulus. Some types of stimuli cause depolarization of the membrane, whereas others cause hyperpolarization. It depends on the specific ion channels that are activated in the cell membrane.

Types of Graded Potentials

For the unipolar cells of sensory neurons—both those with free nerve endings and those within encapsulations—graded potentials develop in the dendrites that influence the generation of an action potential in the axon of the same cell. This is called a **generator potential**. For other sensory receptor cells, such as taste cells or photoreceptors of the retina, graded potentials in their membranes result in the release of neurotransmitters at synapses with sensory neurons. This is called a **receptor potential**.

Synapses

There are two types of connections between electrically active cells, chemical synapses and electrical synapses. In a **chemical synapse**, a chemical signal—namely, a neurotransmitter—is released from one cell and it affects the other cell. In an **electrical synapse**, there is a direct connection between the two cells so that ions can pass directly from one cell to the next. If one cell is depolarized in an electrical synapse, the joined cell also depolarizes because the ions pass between the cells. Chemical synapses involve the transmission of chemical information from one cell to the next. This section will concentrate on the chemical type of synapse.

An example of a chemical synapse is the neuromuscular junction (NMJ) described in the chapter on muscle tissue. In the nervous system, there are many more synapses that are essentially the same as the NMJ. All synapses have common characteristics, which can be summarized in this list:

- presynaptic element
- neurotransmitter (packaged in vesicles)
- synaptic cleft
- receptor proteins
- postsynaptic element
- neurotransmitter elimination or re-uptake

For the NMJ, these characteristics are as follows: the presynaptic element is the motor neuron's axon terminals, the neurotransmitter is acetylcholine, the synaptic cleft is the space between the cells where the neurotransmitter diffuses, the receptor protein is the nicotinic acetylcholine receptor, the postsynaptic element is the sarcolemma of the muscle cell, and the neurotransmitter is eliminated by acetylcholinesterase. Other synapses are similar to this, and the specifics are different, but they all contain the same characteristics.

Neurotransmitter Release

When an action potential reaches the axon terminals, voltage-gated Ca^{2+} channels in the membrane of the synaptic end bulb open. The concentration of Ca^{2+} increases inside the end bulb, and the Ca^{2+} ion associates with proteins in the outer surface of neurotransmitter vesicles. The Ca^{2+} facilitates the merging of the vesicle with the presynaptic membrane so that the neurotransmitter is released through exocytosis into the small gap between the cells, known as the **synaptic cleft**.

Once in the synaptic cleft, the neurotransmitter diffuses the short distance to the postsynaptic membrane and can interact with neurotransmitter receptors. Receptors are specific for the neurotransmitter, and the two fit together like a key and lock. One neurotransmitter binds to its receptor and will not bind to receptors for other neurotransmitters, making the binding a specific chemical event (Figure 12.27).

Another class of neurotransmitter is the **biogenic amine**, a group of neurotransmitters that are enzymatically made from amino acids. They have amino groups in them, but no longer have carboxyl groups and are therefore no longer classified as amino acids. Serotonin is made from tryptophan. It is the basis of the serotonergic system, which has its own specific receptors. Serotonin is transported back into the presynaptic cell for repackaging.

Other biogenic amines are made from tyrosine, and include dopamine, norepinephrine, and epinephrine. Dopamine is part of its own system, the dopaminergic system, which has dopamine receptors. Dopamine is removed from the synapse by transport proteins in the presynaptic cell membrane. Norepinephrine and epinephrine belong to the adrenergic neurotransmitter system. The two molecules are very similar and bind to the same receptors, which are referred to as alpha and beta receptors. Norepinephrine and epinephrine are also transported back into the presynaptic cell. The chemical epinephrine (epi- = "on"; "-nephrine" = kidney) is also known as adrenaline (renal = "kidney"), and norepinephrine is sometimes referred to as noradrenaline. The adrenal gland produces epinephrine and norepinephrine to be released into the blood stream as hormones.

A **neuropeptide** is a neurotransmitter molecule made up of chains of amino acids connected by peptide bonds. This is what a protein is, but the term protein implies a certain length to the molecule. Some neuropeptides are quite short, such as met-enkephalin, which is five amino acids long. Others are long, such as beta-endorphin, which is 31 amino acids long. Neuropeptides are often released at synapses in combination with another neurotransmitter, and they often act as hormones in other systems of the body, such as vasoactive intestinal peptide (VIP) or substance P.

The effect of a neurotransmitter on the postsynaptic element is entirely dependent on the receptor protein. First, if there is no receptor protein in the membrane of the postsynaptic element, then the neurotransmitter has no effect. The depolarizing or hyperpolarizing effect is also dependent on the receptor. When acetylcholine binds to the nicotinic receptor, the postsynaptic cell is depolarized. This is because the receptor is a cation channel and positively charged Na^+ will rush into the cell. However, when acetylcholine binds to the muscarinic receptor, of which there are several variants, it might cause depolarization or hyperpolarization of the target cell.

The amino acid neurotransmitters, glutamate, glycine, and GABA, are almost exclusively associated with just one effect. Glutamate is considered an excitatory amino acid, but only because Glu receptors in the adult cause depolarization of the postsynaptic cell. Glycine and GABA are considered inhibitory amino acids, again because their receptors cause hyperpolarization.

The biogenic amines have mixed effects. For example, the dopamine receptors that are classified as D1 receptors are excitatory whereas D2-type receptors are inhibitory. Biogenic amine receptors and neuropeptide receptors can have even more complex effects because some may not directly affect the membrane potential, but rather have an effect on gene transcription or other metabolic processes in the neuron. The characteristics of the various neurotransmitter systems presented in this section are organized in Table 12.3.

The important thing to remember about neurotransmitters, and signaling chemicals in general, is that the effect is entirely dependent on the receptor. Neurotransmitters bind to one of two classes of receptors at the cell surface, ionotropic or metabotropic (Figure 12.28). Ionotropic receptors are ligand-gated ion channels, such as the nicotinic receptor for acetylcholine or the glycine receptor. A **metabotropic receptor** involves a complex of proteins that result in metabolic changes within the cell. The receptor complex includes the transmembrane receptor protein, a G protein, and an effector protein. The neurotransmitter, referred to as the first messenger, binds to the receptor protein on the extracellular surface of the cell, and the intracellular side of the protein initiates activity of the G protein. The **G protein** is a guanosine triphosphate (GTP) hydrolase that physically moves from the receptor protein to the effector protein to activate the latter. An **effector protein** is an enzyme that catalyzes the generation of a new molecule, which acts as the intracellular mediator of the signal that binds to the receptor. This intracellular mediator is called the second messenger.

Different receptors use different second messengers. Two common examples of second messengers are cyclic adenosine monophosphate (cAMP) and inositol triphosphate (IP_3). The enzyme adenylate cyclase (an example of an effector protein) makes cAMP, and phospholipase C is the enzyme that makes IP_3. Second messengers, after they are produced by the effector protein, cause metabolic changes within the cell. These changes are most likely the activation of other enzymes in the cell. In neurons, they often modify ion channels, either opening or closing them. These enzymes can also cause changes in the cell, such as the activation of genes in the nucleus, and therefore the increased synthesis of proteins. In neurons, these kinds of changes are often the basis of stronger connections

Characteristics of Neurotransmitter Systems

System	Cholinergic	Amino acids	Biogenic amines	Neuropeptides
Neurotransmitters	Acetylcholine	Glutamate, glycine, GABA	Serotonin (5-HT), dopamine, norepinephrine, (epinephrine)	Met-enkephalin, beta-endorphin, VIP, Substance P, etc.
Receptors	Nicotinic and muscarinic receptors	Glu receptors, gly receptors, GABA receptors	5-HT receptors, D1 and D2 receptors, α-adrenergic and β-adrenergic receptors	Receptors are too numerous to list, but are specific to the peptides.
Elimination	Degradation by acetylcholinesterase	Reuptake by neurons or glia	Reuptake by neurons	Degradation by enzymes called peptidases
Postsynaptic effect	Nicotinic receptor causes depolarization. Muscarinic receptors can cause both depolarization or hyperpolarization depending on the subtype.	Glu receptors cause depolarization. Gly and GABA receptors cause hyperpolarization.	Depolarization or hyperpolarization depends on the specific receptor. For example, D1 receptors cause depolarization and D2 receptors cause hyperpolarization.	Depolarization or hyperpolarization depends on the specific receptor.

TABLE 12.3

Disorders of the...

Nervous System

The underlying cause of some neurodegenerative diseases, such as Alzheimer's and Parkinson's, appears to be related to proteins—specifically, to proteins behaving badly. One of the strongest theories of what causes Alzheimer's disease is based on the accumulation of beta-amyloid plaques, dense conglomerations of a protein that is not functioning correctly. Parkinson's disease is linked to an increase in a protein known as alpha-synuclein that is toxic to the cells of the substantia nigra nucleus in the midbrain.

For proteins to function correctly, they are dependent on their three-dimensional shape. The linear sequence of amino acids folds into a three-dimensional shape that is based on the interactions between and among those amino acids. When the folding is disturbed, and proteins take on a different shape, they stop functioning correctly. But the disease is not necessarily the result of functional loss of these proteins; rather, these altered proteins start to accumulate and may become toxic. For example, in Alzheimer's, the hallmark of the disease is the accumulation of these amyloid plaques in the cerebral cortex. The term coined to describe this sort of disease is "proteopathy" and it includes other diseases. Creutzfeld-Jacob disease, the human variant of the prion disease known as mad cow disease in the bovine, also involves the accumulation of amyloid plaques, similar to Alzheimer's. Diseases of other organ systems can fall into this group as well, such as cystic fibrosis or type 2 diabetes. Recognizing the relationship between these diseases has suggested new therapeutic possibilities. Interfering with the accumulation of the proteins, and possibly as early as their original production within the cell, may unlock new ways to alleviate these devastating diseases.

that physically moves from the receptor protein to the effector protein to activate the latter

ganglion localized collection of neuron cell bodies in the peripheral nervous system

gated property of a channel that determines how it opens under specific conditions, such as voltage change or physical deformation

generator potential graded potential from dendrites of a unipolar cell which generates the action potential in the initial segment of that cell's axon

glial cell one of the various types of neural tissue cells responsible for maintenance of the tissue, and largely responsible for supporting neurons

graded potential change in the membrane potential that varies in size, depending on the size of the stimulus that elicits it

gray matter regions of the nervous system containing cell bodies of neurons with few or no myelinated axons; actually may be more pink or tan in color, but called gray in contrast to white matter

inactivation gate part of a voltage-gated Na^+ channel that closes when the membrane potential reaches +30 mV

inhibitory postsynaptic potential (IPSP) graded potential in the postsynaptic membrane that is the result of hyperpolarization and makes an action potential less likely to occur

initial segment first part of the axon as it emerges from the axon hillock, where the electrical signals known as action potentials are generated

integration nervous system function that combines sensory perceptions and higher cognitive functions (memories, learning, emotion, etc.) to produce a response

ionotropic receptor neurotransmitter receptor that acts as an ion channel gate, and opens by the binding of the neurotransmitter

leakage channel ion channel that opens randomly and is not gated to a specific event, also known as a non-gated channel

ligand-gated channels another name for an ionotropic receptor for which a neurotransmitter is the ligand

lower motor neuron second neuron in the motor command pathway that is directly connected to the skeletal muscle

mechanically gated channel ion channel that opens when a physical event directly affects the structure of the protein

membrane potential distribution of charge across the cell membrane, based on the charges of ions

metabotropic receptor neurotransmitter receptor that involves a complex of proteins that cause metabolic changes in a cell

microglia glial cell type in the CNS that serves as the resident component of the immune system

multipolar shape of a neuron that has multiple processes—the axon and two or more dendrites

muscarinic receptor type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

myelin lipid-rich insulating substance surrounding the axons of many neurons, allowing for faster transmission of electrical signals

myelin sheath lipid-rich layer of insulation that surrounds an axon, formed by oligodendrocytes in the CNS and Schwann cells in the PNS; facilitates the transmission of electrical signals

nerve cord-like bundle of axons located in the peripheral nervous system that transmits sensory input and response output to and from the central nervous system

neuron neural tissue cell that is primarily responsible for generating and propagating electrical signals into, within, and out of the nervous system

neuropeptide neurotransmitter type that includes protein molecules and shorter chains of amino acids

neurotransmitter chemical signal that is released from the synaptic end bulb of a neuron to cause a change in the target cell

nicotinic receptor type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

node of Ranvier gap between two myelinated regions of an axon, allowing for strengthening of the electrical signal as it propagates down the axon

nonspecific channel channel that is not specific to one ion over another, such as a nonspecific cation channel that allows any positively charged ion across the membrane

nucleus in the nervous system, a localized collection of neuron cell bodies that are functionally related; a "center" of neural function

oligodendrocyte glial cell type in the CNS that provides the myelin insulation for axons in tracts

peripheral nervous system (PNS) anatomical division of the nervous system that is largely outside the cranial and vertebral cavities, namely all parts except the brain and spinal cord

postsynaptic potential (PSP) graded potential in the postsynaptic membrane caused by the binding of neurotransmitter to protein receptors

precentral gyrus of the frontal cortex region of the cerebral cortex responsible for generating motor commands, where the upper motor neuron cell body is located

Chapter Review

12.1 Basic Structure and Function of the Nervous System

The nervous system can be separated into divisions on the basis of anatomy and physiology. The anatomical divisions are the central and peripheral nervous systems. The CNS is the brain and spinal cord. The PNS is everything else. Functionally, the nervous system can be divided into those regions that are responsible for sensation, those that are responsible for integration, and those that are responsible for generating responses. All of these functional areas are found in both the central and peripheral anatomy.

Considering the anatomical regions of the nervous system, there are specific names for the structures within each division. A localized collection of neuron cell bodies is referred to as a nucleus in the CNS and as a ganglion in the PNS. A bundle of axons is referred to as a tract in the CNS and as a nerve in the PNS. Whereas nuclei and ganglia are specifically in the central or peripheral divisions, axons can cross the boundary between the two. A single axon can be part of a nerve and a tract. The name for that specific structure depends on its location.

Nervous tissue can also be described as gray matter and white matter on the basis of its appearance in unstained tissue. These descriptions are more often used in the CNS. Gray matter is where nuclei are found and white matter is where tracts are found. In the PNS, ganglia are basically gray matter and nerves are white matter.

The nervous system can also be divided on the basis of how it controls the body. The somatic nervous system (SNS) is responsible for functions that result in moving skeletal muscles. Any sensory or integrative functions that result in the movement of skeletal muscle would be considered somatic. The autonomic nervous system (ANS) is responsible for functions that affect cardiac or smooth muscle tissue, or that cause glands to produce their secretions. Autonomic functions are distributed between central and peripheral regions of the nervous system. The sensations that lead to autonomic functions can be the same sensations that are part of initiating somatic responses. Somatic and autonomic integrative functions may overlap as well.

A special division of the nervous system is the enteric nervous system, which is responsible for controlling the digestive organs. Parts of the autonomic nervous system overlap with the enteric nervous system. The enteric nervous system is exclusively found in the periphery because it is the nervous tissue in the organs of the digestive system.

12.2 Nervous Tissue

Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical signals. Glial cells are supporting cells, maintaining the environment around the neurons.

Neurons are polarized cells, based on the flow of electrical signals along their membrane. Signals are received at the dendrites, are passed along the cell body, and propagate along the axon towards the target, which may be another neuron, muscle tissue, or a gland. Many axons are insulated by a lipid-rich substance called myelin. Specific types of glial cells provide this insulation.

Several types of glial cells are found in the nervous system, and they can be categorized by the anatomical division in which they are found. In the CNS, astrocytes, oligodendrocytes, microglia, and ependymal cells are found. Astrocytes are important for maintaining the chemical environment around the neuron and are crucial for regulating the blood-brain barrier. Oligodendrocytes are the myelinating glia in the CNS. Microglia act as phagocytes and play a role in immune surveillance. Ependymal cells are responsible for filtering the blood to produce cerebrospinal fluid, which is a circulatory fluid that performs some of the functions of blood in the brain and spinal cord because of the BBB. In the PNS, satellite cells are supporting cells for the neurons, and Schwann cells insulate peripheral axons.

12.3 The Function of Nervous Tissue

Sensation starts with the activation of a sensory ending, such as the thermoreceptor in the skin sensing the temperature of the water. The sensory endings in the skin initiate an electrical signal that travels along the sensory axon within a nerve into the spinal cord, where it synapses with a neuron in the gray matter of the spinal cord. The temperature information represented in that electrical signal is passed to the next neuron by a chemical signal that diffuses across the small gap of the synapse and initiates a new electrical signal in the target cell. That signal travels through the sensory pathway to the brain, passing through the thalamus, where conscious perception of the water temperature is made possible by the cerebral cortex. Following integration of that information with other cognitive processes and sensory

Interactive Link Questions

1. In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize website (http://openstax.org/l/nobel_2) to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from x-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?
2. Visit this site (http://openstax.org/l/troublewstairs) to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?
3. The neurons are dynamic cells with the ability to make a vast number of connections and to respond incredibly quickly to stimuli and to initiate movements based on those stimuli. They are the focus of intense research as failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Why wouldn't they be helpful for plants or microorganisms?
4. View the University of Michigan Webscope (http://openstax.org/l/nervefiber) to see an electron micrograph of a cross-section of a myelinated nerve fiber. The axon contains microtubules and neurofilaments, bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain that makes them the deep, dark, black color, such as the multiple layers that are the myelin sheath?
5. What happens across the membrane of an electrically active cell is a dynamic process that is hard to visualize with static images or through text descriptions. View this animation (http://openstax.org/l/dynamic1) to really understand the process. What is the difference between the driving force for Na^+ and K^+? And what is similar about the movement of these two ions?
6. Visit this site (http://openstax.org/l/neurolab) to see a virtual neurophysiology lab, and to observe electrophysiological processes in the nervous system, where scientists directly measure the electrical signals produced by neurons. Often, the action potentials occur so rapidly that watching a screen to see them occur is not helpful. A speaker is powered by the signals recorded from a neuron and it "pops" each time the neuron fires an action potential. These action potentials are firing so fast that it sounds like static on the radio. Electrophysiologists can recognize the patterns within that static to understand what is happening. Why is the leech model used for measuring the electrical activity of neurons instead of using humans?
7. Watch this video (http://openstax.org/l/summation) to learn about summation. The process of converting electrical signals to chemical signals and back requires subtle changes that can result in transient increases or decreases in membrane voltage. To cause a lasting change in the target cell, multiple signals are usually added together, or summated. Does spatial summation have to happen all at once, or can the separate signals arrive on the postsynaptic neuron at slightly different times? Explain your answer.
8. Watch this video (http://openstax.org/l/neurotrans) to learn about the release of a neurotransmitter. The action potential reaches the end of the axon, called the axon terminal, and a chemical signal is released to tell the target cell to do something, either initiate a new action potential, or to suppress that activity. In a very short space, the electrical signal of the action potential is changed into the chemical signal of a neurotransmitter, and then back to electrical changes in the target cell membrane. What is the importance of voltage-gated calcium channels in the release of neurotransmitters?

23. What ion enters a neuron causing depolarization of the cell membrane?
   a. sodium
   b. chloride
   c. potassium
   d. phosphate

24. Voltage-gated Na^+ channels open upon reaching what state?
   a. resting potential
   b. threshold
   c. repolarization
   d. overshoot

25. What does a ligand-gated channel require in order to open?
   a. increase in concentration of Na^+ ions
   b. binding of a neurotransmitter
   c. increase in concentration of K^+ ions
   d. depolarization of the membrane

26. What does a mechanically gated channel respond to?
   a. physical stimulus
   b. chemical stimulus
   c. increase in resistance
   d. decrease in resistance

27. Which of the following voltages would most likely be measured during the relative refractory period?
   a. +30 mV
   b. 0 mV
   c. -45 mV
   d. -80 mv

28. Which of the following is probably going to propagate an action potential fastest?
   a. a thin, unmyelinated axon
   b. a thin, myelinated axon
   c. a thick, unmyelinated axon
   d. a thick, myelinated axon

29. How much of a change in the membrane potential is necessary for the summation of postsynaptic potentials to result in an action potential being generated?
   a. +30 mV
   b. +15 mV
   c. +10 mV
   d. -15 mV

30. A channel opens on a postsynaptic membrane that causes a negative ion to enter the cell. What type of graded potential is this?
   a. depolarizing
   b. repolarizing
   c. hyperpolarizing
   d. non-polarizing

31. What neurotransmitter is released at the neuromuscular junction?
   a. norepinephrine
   b. serotonin
   c. dopamine
   d. acetylcholine

32. What type of receptor requires an effector protein to initiate a signal?
   a. biogenic amine
   b. ionotropic receptor
   c. cholinergic system
   d. metabotropic receptor

33. Which of the following neurotransmitters is associated with inhibition exclusively?
   a. GABA
   b. acetylcholine
   c. glutamate
   d. norepinephrine

Critical Thinking Questions

34. What responses are generated by the nervous system when you run on a treadmill? Include an example of each type of tissue that is under nervous system control.

35. When eating food, what anatomical and functional divisions of the nervous system are involved in the perceptual experience?

36. Multiple sclerosis is a demyelinating disease affecting the central nervous system. What type of cell would be the most likely target of this disease? Why?

37. Which type of neuron, based on its shape, is best suited for relaying information directly from one neuron to another? Explain why.

38. Sensory fibers, or pathways, are referred to as "afferent." Motor fibers, or pathways, are referred to as "efferent." What can you infer about the meaning of these two terms (afferent and efferent) in a structural or anatomical context?

39. If a person has a motor disorder and cannot move their arm voluntarily, but their muscles have tone, which motor neuron—upper or lower—is probably affected? Explain why.

13.1 The Embryologic Perspective

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the growth and differentiation of the neural tube
- Relate the different stages of development to the adult structures of the central nervous system
- Explain the expansion of the ventricular system of the adult brain from the central canal of the neural tube
- Describe the connections of the diencephalon and cerebellum on the basis of patterns of embryonic development

The brain is a complex organ composed of gray parts and white matter, which can be hard to distinguish. Starting from an embryologic perspective allows you to understand more easily how the parts relate to each other. The embryonic nervous system begins as a very simple structure—essentially just a straight line, which then gets increasingly complex. Looking at the development of the nervous system with a couple of early snapshots makes it easier to understand the whole complex system.

Many structures that appear to be adjacent in the adult brain are not connected, and the connections that exist may seem arbitrary. But there is an underlying order to the system that comes from how different parts develop. By following the developmental pattern, it is possible to learn what the major regions of the nervous system are.

The Neural Tube

To begin, a sperm cell and an egg cell fuse to become a fertilized egg. The fertilized egg cell, or zygote, starts dividing to generate the cells that make up an entire organism. Sixteen days after fertilization, the developing embryo's cells belong to one of three germ layers that give rise to the different tissues in the body. The endoderm, or inner tissue, is responsible for generating the lining tissues of various spaces within the body, such as the mucosae of the digestive and respiratory systems. The mesoderm, or middle tissue, gives rise to most of the muscle and connective tissues. Finally the ectoderm, or outer tissue, develops into the integumentary system (the skin) and the nervous system. It is probably not difficult to see that the outer tissue of the embryo becomes the outer covering of the body. But how is it responsible for the nervous system?

As the embryo develops, a portion of the ectoderm differentiates into a specialized region of neuroectoderm, which is the precursor for the tissue of the nervous system. Molecular signals induce cells in this region to differentiate into the neuroepithelium, forming a **neural plate**. The cells then begin to change shape, causing the tissue to buckle and fold inward (Figure 13.2). A **neural groove** forms, visible as a line along the dorsal surface of the embryo. The ridge-like edge on either side of the neural groove is referred as the **neural fold**. As the neural folds come together and converge, the underlying structure forms into a tube just beneath the ectoderm called the **neural tube**. Cells from the neural folds then separate from the ectoderm to form a cluster of cells referred to as the **neural crest**, which runs lateral to the neural tube. The neural crest migrates away from the nascent, or embryonic, central nervous system (CNS) that will form along the neural groove and develops into several parts of the peripheral nervous system (PNS), including the enteric nervous tissue. Many tissues that are not part of the nervous system also arise from the neural crest, such as craniofacial cartilage and bone, and melanocytes.

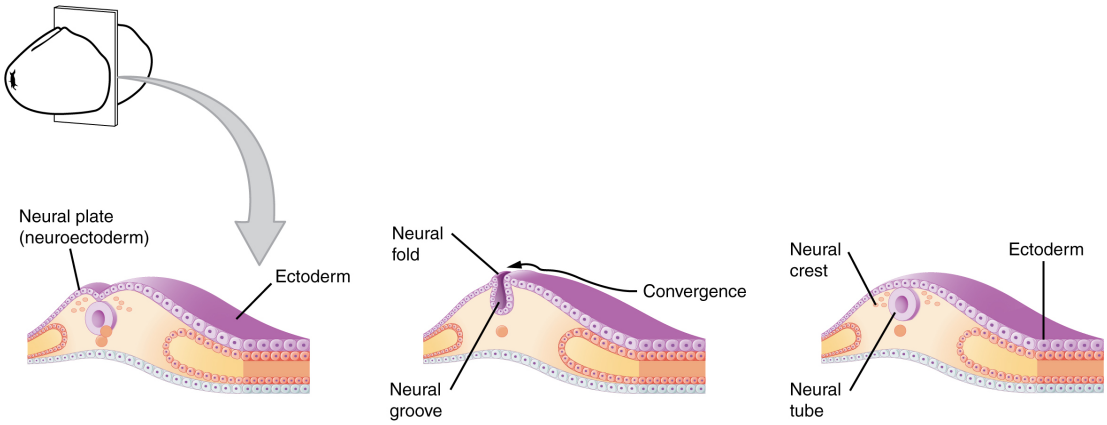


FIGURE 13.2 Early Embryonic Development of Nervous System The neuroectoderm begins to fold inward to form the neural groove.

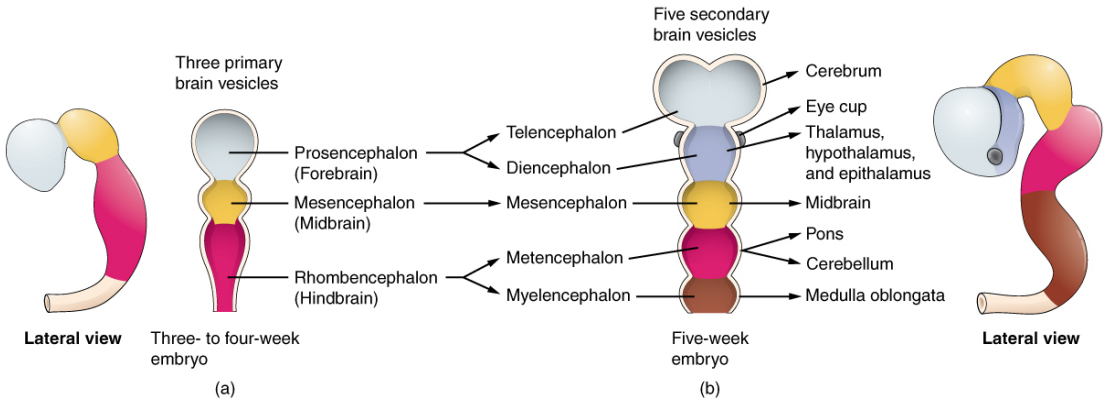


FIGURE 13.3 Primary and Secondary Vesicle Stages of Development The embryonic brain develops complexity through enlargements of the neural tube called vesicles; (a) The primary vesicle stage has three regions, and (b) the secondary vesicle stage has five regions.

INTERACTIVE LINK

Watch this animation (http://openstax.org/l/braindevel) to examine the development of the brain, starting with the neural tube. As the anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?

Spinal Cord Development

While the brain is developing from the anterior neural tube, the spinal cord is developing from the posterior neural tube. However, its structure does not differ from the basic layout of the neural tube. It is a long, straight cord with a small, hollow space down the center. The neural tube is defined in terms of its anterior versus posterior portions, but it also has a dorsal–ventral dimension. As the neural tube separates from the rest of the ectoderm, the side closest to the surface is dorsal, and the deeper side is ventral.

As the spinal cord develops, the cells making up the wall of the neural tube proliferate and differentiate into the neurons and glia of the spinal cord. The dorsal tissues will be associated with sensory functions, and the ventral tissues will be associated with motor functions.

Relating Embryonic Development to the Adult Brain

Embryonic development can help in understanding the structure of the adult brain because it establishes a framework on which more complex structures can be built. First, the neural tube establishes the anterior–posterior dimension of the nervous system, which is called the **neuraxis**. The embryonic nervous system in mammals can be said to have a standard arrangement. Humans (and other primates, to some degree) make this complicated by standing up and walking on two legs. The anterior–posterior dimension of the neuraxis overlays the superior–inferior dimension of the body. However, there is a major curve between the brain stem and forebrain, which is called the **cephalic flexure**. Because of this, the neuraxis starts in an inferior position—the end of the spinal cord—and ends in an anterior position, the front of the cerebrum. If this is confusing, just imagine a four-legged animal standing up on two legs. Without the flexure in the brain stem, and at the top of the neck, that animal would be looking straight up instead of straight in front (Figure 13.4).

Stages of Embryonic Development

Neural tube	Primary vesicle stage	Secondary vesicle stage	Adult structures	Ventricles
Anterior neural tube	Prosencephalon	Telencephalon	Cerebrum	Lateral ventricles
Anterior neural tube	Prosencephalon	Diencephalon	Diencephalon	Third ventricle
Anterior neural tube	Mesencephalon	Mesencephalon	Midbrain	Cerebral aqueduct
Anterior neural tube	Rhombencephalon	Metencephalon	Pons cerebellum	Fourth ventricle
Anterior neural tube	Rhombencephalon	Myelencephalon	Medulla	Fourth ventricle
Posterior neural tube			Spinal cord	Central canal

TABLE 13.1

Disorders of the...

Nervous System

Early formation of the nervous system depends on the formation of the neural tube. A groove forms along the dorsal surface of the embryo, which becomes deeper until its edges meet and close off to form the tube. If this fails to happen, especially in the posterior region where the spinal cord forms, a developmental defect called spina bifida occurs. The closing of the neural tube is important for more than just the proper formation of the nervous system. The surrounding tissues are dependent on the correct development of the tube. The connective tissues surrounding the CNS can be involved as well.

There are three classes of this disorder: occulta, meningocele, and myelomeningocele (Figure 13.5). The first type, spina bifida occulta, is the mildest because the vertebral bones do not fully surround the spinal cord, but the spinal cord itself is not affected. No functional differences may be noticed, which is what the word occulta means; it is hidden spina bifida. The other two types both involve the formation of a cyst—a fluid-filled sac of the connective tissues that cover the spinal cord called the meninges. “Meningocele” means that the meninges protrude through the spinal column but nerves may not be involved and few symptoms are present, though complications may arise later in life. “Myelomeningocele” means that the meninges protrude and spinal nerves are involved, and therefore severe neurological symptoms can be present.

Often surgery to close the opening or to remove the cyst is necessary. The earlier that surgery can be performed, the better the chances of controlling or limiting further damage or infection at the opening. For many children with meningocele, surgery will alleviate the pain, although they may experience some functional loss. Because the myelomeningocele form of spina bifida involves more extensive damage to the nervous tissue, neurological damage may persist, but symptoms can often be handled. Complications of the spinal cord may present later in life, but overall life expectancy is not reduced.

The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum** (Figure 13.6). The wrinkled portion is the **cerebral cortex**, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, a right and left **cerebral hemisphere**. Deep within the cerebrum, the white matter of the **corpus callosum** provides the major pathway for communication between the two hemispheres of the cerebral cortex.

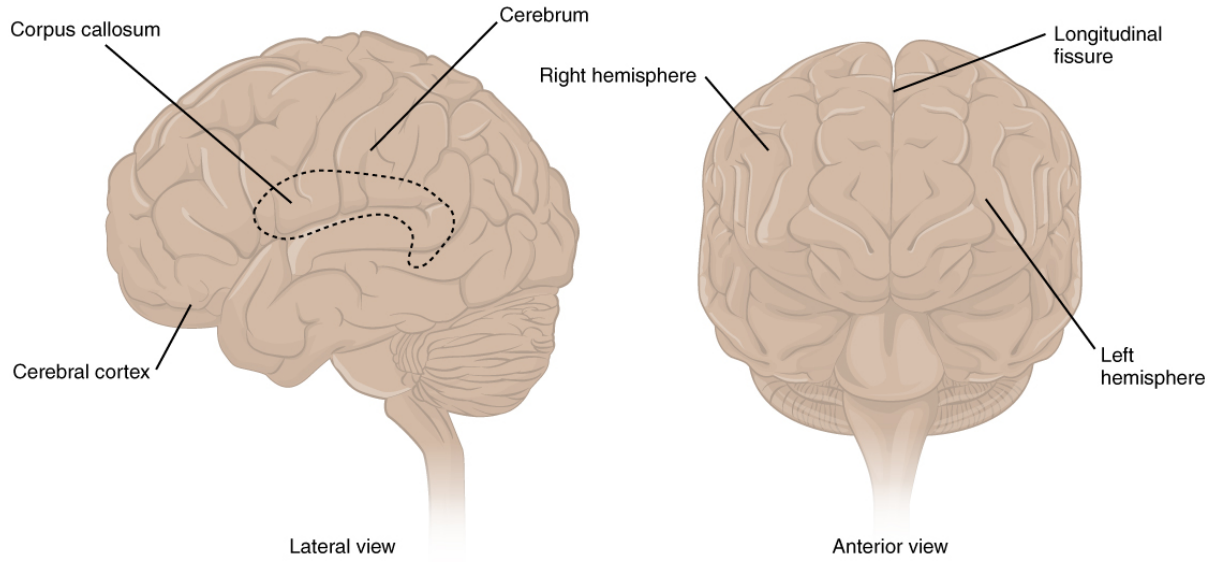


FIGURE 13.6 The Cerebrum The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning "bark of a tree") and several deep nuclei that belong to three important functional groups. The **basal nuclei** are responsible for cognitive processing, the most important function being that associated with planning movements. The **basal forebrain** contains nuclei that are important in learning and memory. The **limbic cortex** is the region of the cerebral cortex that is part of the **limbic system**, a collection of structures involved in emotion, memory, and behavior.

Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the cerebral cortex. This thin, extensive region of wrinkled gray matter is responsible for the higher functions of the nervous system. A **gyrus** (plural = gyri) is the ridge of one of those wrinkles, and a **sulcus** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex.

The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter.

The folding of the cortex maximizes the amount of gray matter in the cranial cavity. During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone's brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes (Figure 13.7). The **lateral sulcus** that separates the **temporal lobe** from the other regions is one such landmark. Superior to the lateral sulcus are the **parietal lobe** and **frontal lobe**, which are separated from each other by the **central sulcus**. The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an

the basis of personality, short-term memory, and consciousness. The prefrontal lobotomy is an outdated mode of treatment for personality disorders (psychiatric conditions) that profoundly affected the personality of the patient.

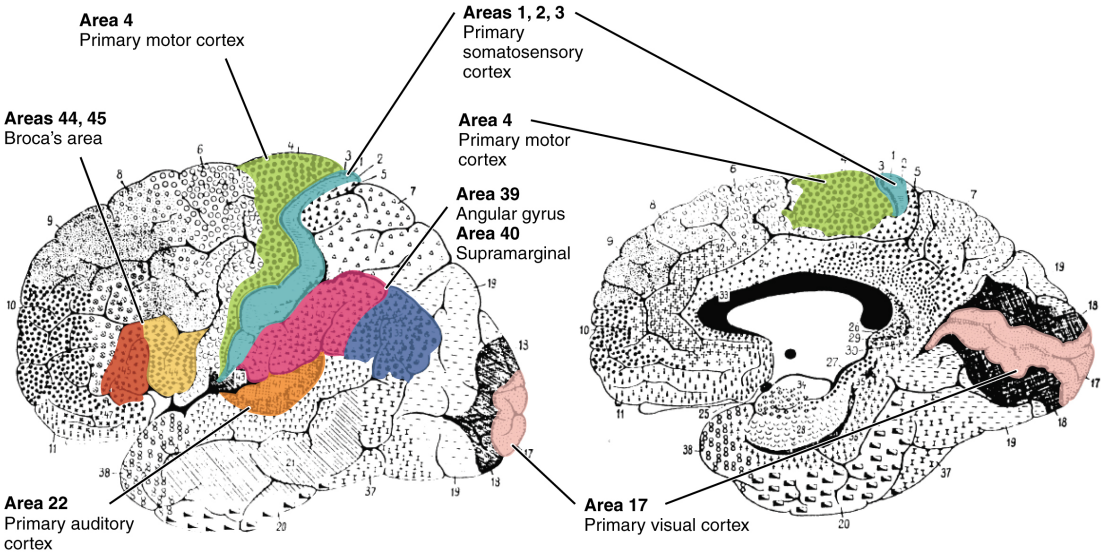


FIGURE 13.8 Brodmann's Areas of the Cerebral Cortex Brodmann mapping of functionally distinct regions of the cortex was based on its cytoarchitecture at a microscopic level.

Subcortical structures

Beneath the cerebral cortex are sets of nuclei known as **subcortical nuclei** that augment cortical processes. The nuclei of the basal forebrain serve as the primary location for acetylcholine production, which modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain. The **hippocampus** and **amygdala** are medial-lobe structures that, along with the adjacent cortex, are involved in long-term memory formation and emotional responses. The basal nuclei are a set of nuclei in the cerebrum responsible for comparing cortical processing with the general state of activity in the nervous system to influence the likelihood of movement taking place. For example, while a student is sitting in a classroom listening to a lecture, the basal nuclei will keep the urge to jump up and scream from actually happening. (The basal nuclei are also referred to as the basal ganglia, although that is potentially confusing because the term ganglia is typically used for peripheral structures.)

The major structures of the basal nuclei that control movement are the **caudate**, **putamen**, and **globus pallidus**, which are located deep in the cerebrum. The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe. The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the **striatum**. The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively. These nuclei are depicted in a frontal section of the brain in Figure 13.9.

external segment (GPe), and subthalamic nucleus (STN).

The switch between the two pathways is the **substantia nigra pars compacta**, which projects to the striatum and releases the neurotransmitter dopamine. Dopamine receptors are either excitatory (D1-type receptors) or inhibitory (D2-type receptors). The direct pathway is activated by dopamine, and the indirect pathway is inhibited by dopamine. When the substantia nigra pars compacta is firing, it signals to the basal nuclei that the body is in an active state, and movement will be more likely. When the substantia nigra pars compacta is silent, the body is in a passive state, and movement is inhibited. To illustrate this situation, while a student is sitting listening to a lecture, the substantia nigra pars compacta would be silent and the student less likely to get up and walk around. Likewise, while the professor is lecturing, and walking around at the front of the classroom, the professor's substantia nigra pars compacta would be active, in keeping with their activity level.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/basalnuclei1) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in "disinhibition" of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

INTERACTIVE LINK

Watch this video (http://openstax.org/l/basalnuclei2) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

Everyday Connection

The Myth of Left Brain/Right Brain

There is a persistent myth that people are "right-brained" or "left-brained," which is an oversimplification of an important concept about the cerebral hemispheres. There is some lateralization of function, in which the left side of the brain is devoted to language function and the right side is devoted to spatial and nonverbal reasoning. Whereas these functions are predominantly associated with those sides of the brain, there is no monopoly by either side on these functions. Many pervasive functions, such as language, are distributed globally around the cerebrum.

Some of the support for this misconception has come from studies of split brains. A drastic way to deal with a rare and devastating neurological condition (intractable epilepsy) is to separate the two hemispheres of the brain. After sectioning the corpus callosum, a split-brained patient will have trouble producing verbal responses on the basis of sensory information processed on the right side of the cerebrum, leading to the idea that the left side is responsible for language function.

However, there are well-documented cases of language functions lost from damage to the right side of the brain. The deficits seen in damage to the left side of the brain are classified as aphasia, a loss of speech function; damage on the right side can affect the use of language. Right-side damage can result in a loss of ability to understand figurative aspects of speech, such as jokes, irony, or metaphors. Nonverbal aspects of speech can be affected by damage to the right side, such as facial expression or body language, and right-side damage can lead to a "flat affect" in speech, or a loss of emotional expression in speech—sounding like a robot when talking.

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to "through brain." It is the connection between the cerebrum and

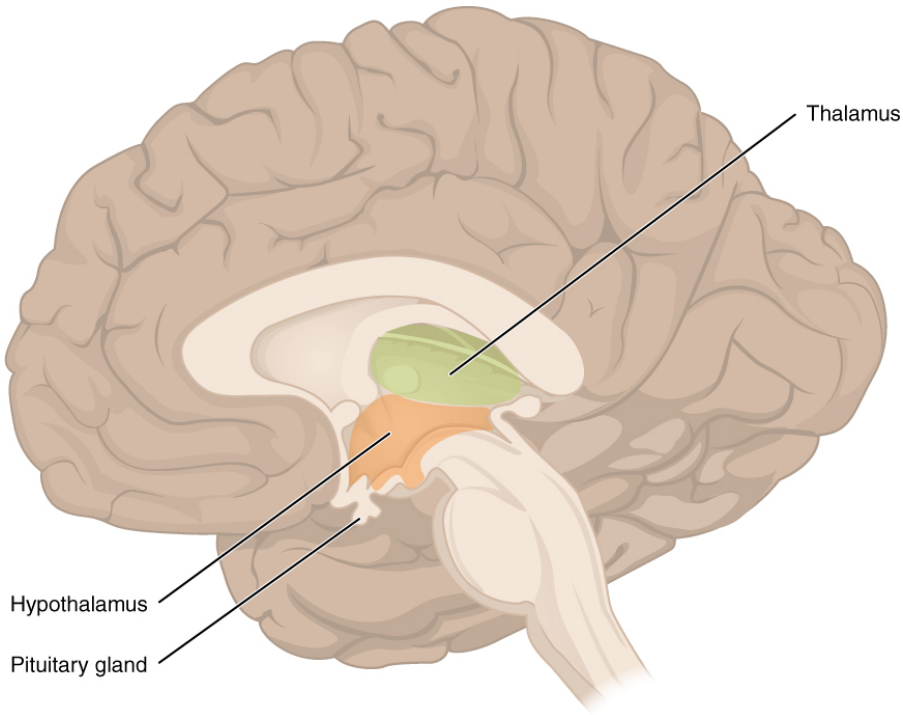


FIGURE 13.11 The Diencephalon The diencephalon is composed primarily of the thalamus and hypothalamus, which together define the walls of the third ventricle. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.

Brain Stem

The midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain stem (Figure 13.12). The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a separate region of the adult brain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates.

The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

and attention.

The Cerebellum

The **cerebellum**, as the name suggests, is the "little brain." It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain (Figure 13.13). The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.

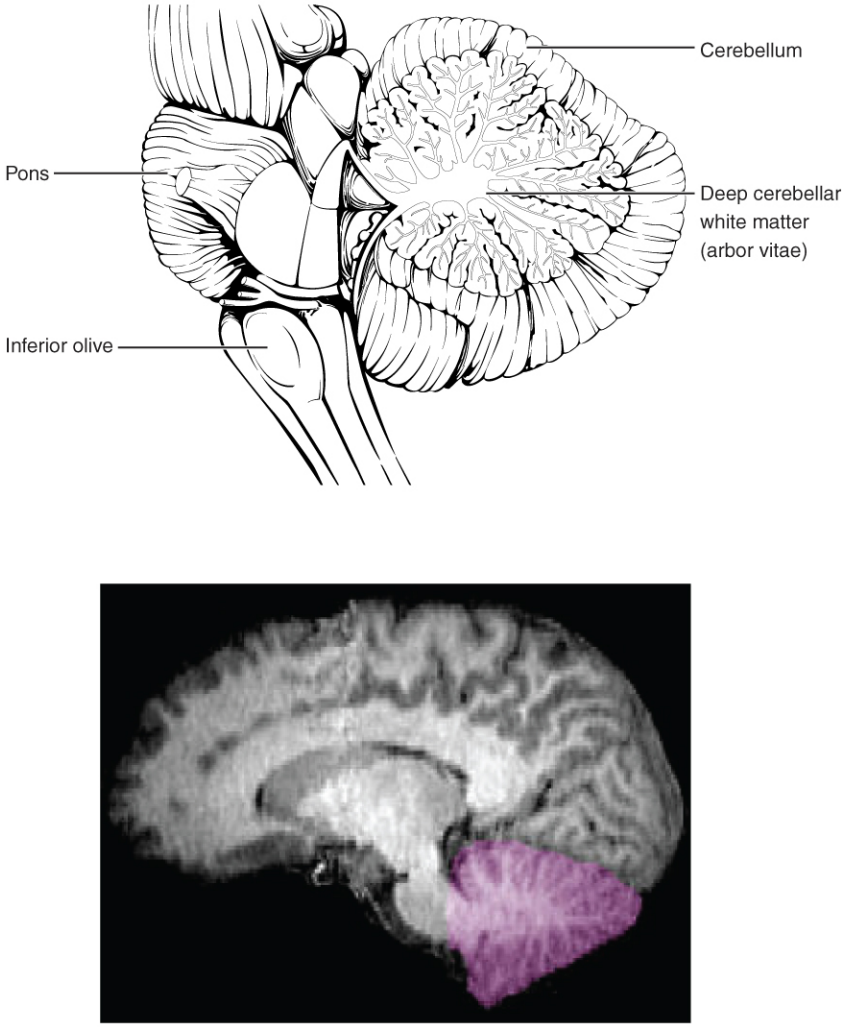


FIGURE 13.13 The Cerebellum The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the **inferior olive**. Fibers from this nucleus enter the cerebellum and are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

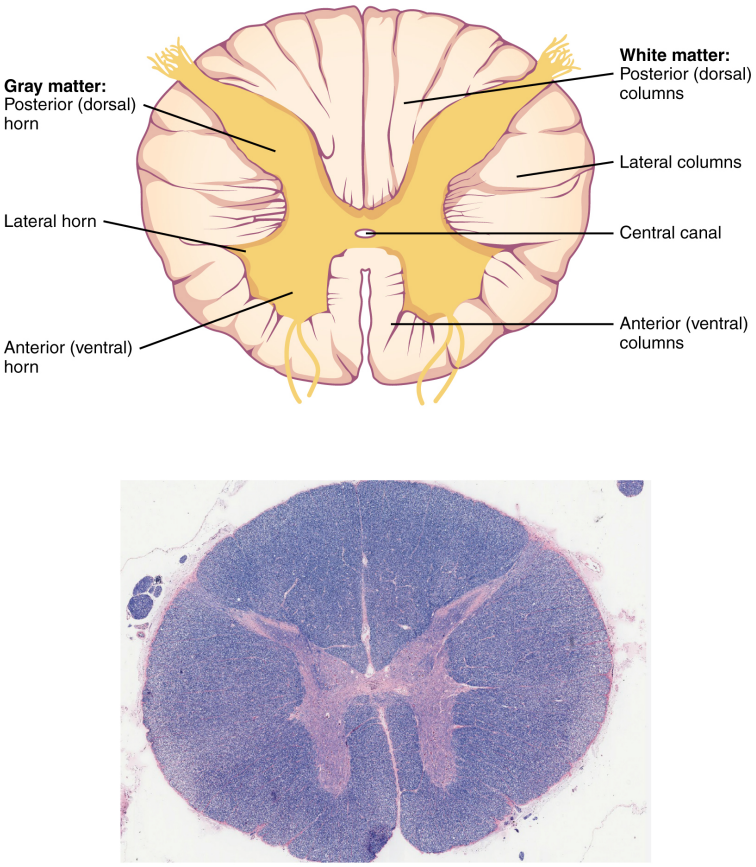


FIGURE 13.14 Cross-section of Spinal Cord The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. **Ascending tracts** of nervous system fibers in these columns carry sensory information up to the brain, whereas **descending tracts** carry motor commands from the brain. Looking at the spinal cord longitudinally, the columns extend along its length as continuous bands of white matter. Between the two posterior horns of gray matter are the **posterior columns**. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the **anterior columns**. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the **lateral columns**. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/graymatter) to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

Disorders of the...

Basal Nuclei

Parkinson's disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the

Arterial Supply

The major artery carrying recently oxygenated blood away from the heart is the aorta. The very first branches off the aorta supply the heart with nutrients and oxygen. The next branches give rise to the **common carotid arteries**, which further branch into the **internal carotid arteries**. The external carotid arteries supply blood to the tissues on the surface of the cranium. The bases of the common carotids contain stretch receptors that immediately respond to the drop in blood pressure upon standing. The **orthostatic reflex** is a reaction to this change in body position, so that blood pressure is maintained against the increasing effect of gravity (orthostatic means "standing up"). Heart rate increases—a reflex of the sympathetic division of the autonomic nervous system—and this raises blood pressure.

The internal carotid artery enters the cranium through the **carotid canal** in the temporal bone. A second set of vessels that supply the CNS are the **vertebral arteries**, which are protected as they pass through the neck region by the transverse foramina of the cervical vertebrae. The vertebral arteries enter the cranium through the **foramen magnum** of the occipital bone. Branches off the left and right vertebral arteries merge into the **anterior spinal artery** supplying the anterior aspect of the spinal cord, found along the anterior median fissure. The two vertebral arteries then merge into the **basilar artery**, which gives rise to branches to the brain stem and cerebellum. The left and right internal carotid arteries and branches of the basilar artery all become the **circle of Willis**, a confluence of arteries that can maintain perfusion of the brain even if narrowing or a blockage limits flow through one part (Figure 13.15).

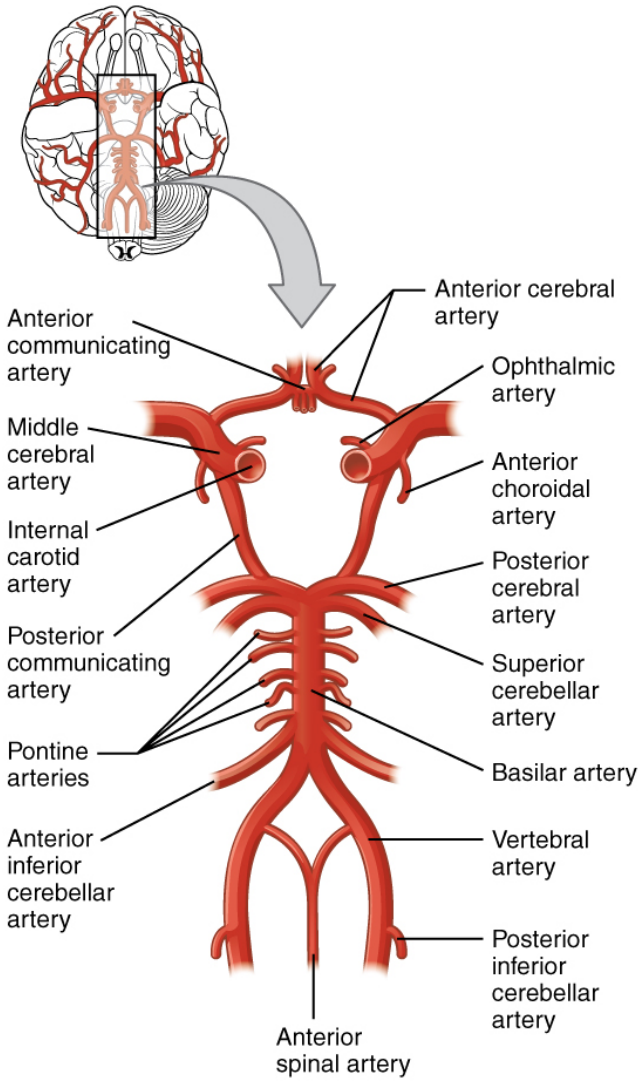


FIGURE 13.15 Circle of Willis The blood supply to the brain enters through the internal carotid arteries and the vertebral arteries, eventually giving rise to the circle of Willis.

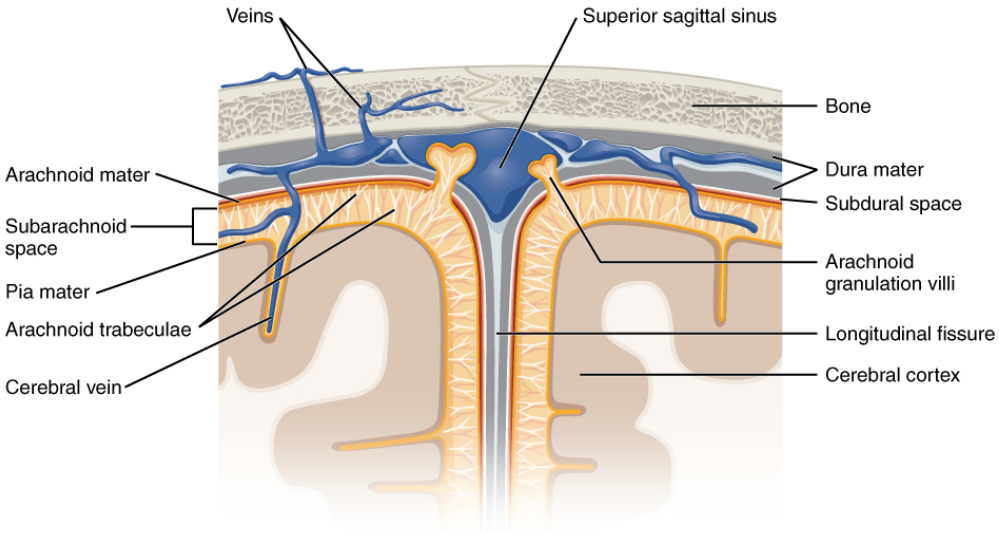


FIGURE 13.17 Meningeal Layers of Superior Sagittal Sinus The layers of the meninges in the longitudinal fissure of the superior sagittal sinus are shown, with the dura mater adjacent to the inner surface of the cranium, the pia mater adjacent to the surface of the brain, and the arachnoid and subarachnoid space between them. An arachnoid villus is shown emerging into the dural sinus to allow CSF to filter back into the blood for drainage.

Dura Mater

Like a thick cap covering the brain, the dura mater is a tough outer covering. The name comes from the Latin for "tough mother" to represent its physically protective role. It encloses the entire CNS and the major blood vessels that enter the cranium and vertebral cavity. It is directly attached to the inner surface of the bones of the cranium and to the very end of the vertebral cavity.

There are infoldings of the dura that fit into large crevasses of the brain. Two infoldings go through the midline separations of the cerebrum and cerebellum; one forms a shelf-like tent between the occipital lobes of the cerebrum and the cerebellum, and the other surrounds the pituitary gland. The dura also surrounds and supports the venous sinuses.

Arachnoid Mater

The middle layer of the meninges is the arachnoid, named for the spider-web–like trabeculae between it and the pia mater. The arachnoid defines a sac-like enclosure around the CNS. The trabeculae are found in the **subarachnoid space**, which is filled with circulating CSF. The arachnoid emerges into the dural sinuses as the **arachnoid granulations**, where the CSF is filtered back into the blood for drainage from the nervous system.

The subarachnoid space is filled with circulating CSF, which also provides a liquid cushion to the brain and spinal cord. Similar to clinical blood work, a sample of CSF can be withdrawn to find chemical evidence of neuropathology or metabolic traces of the biochemical functions of nervous tissue.

Pia Mater

The outer surface of the CNS is covered in the thin fibrous membrane of the pia mater. It is thought to have a continuous layer of cells providing a fluid-impermeable membrane. The name pia mater comes from the Latin for "tender mother," suggesting the thin membrane is a gentle covering for the brain. The pia extends into every convolution of the CNS, lining the inside of the sulci in the cerebral and cerebellar cortices. At the end of the spinal cord, a thin filament extends from the inferior end of CNS at the upper lumbar region of the vertebral column to the sacral end of the vertebral column. Because the spinal cord does not extend through the lower lumbar region of the vertebral column, a needle can be inserted through the dura and arachnoid layers to withdraw CSF. This procedure is called a **lumbar puncture** and avoids the risk of damaging the central tissue of the spinal cord. Blood vessels that are nourishing the central nervous tissue are between the pia mater and the nervous tissue.

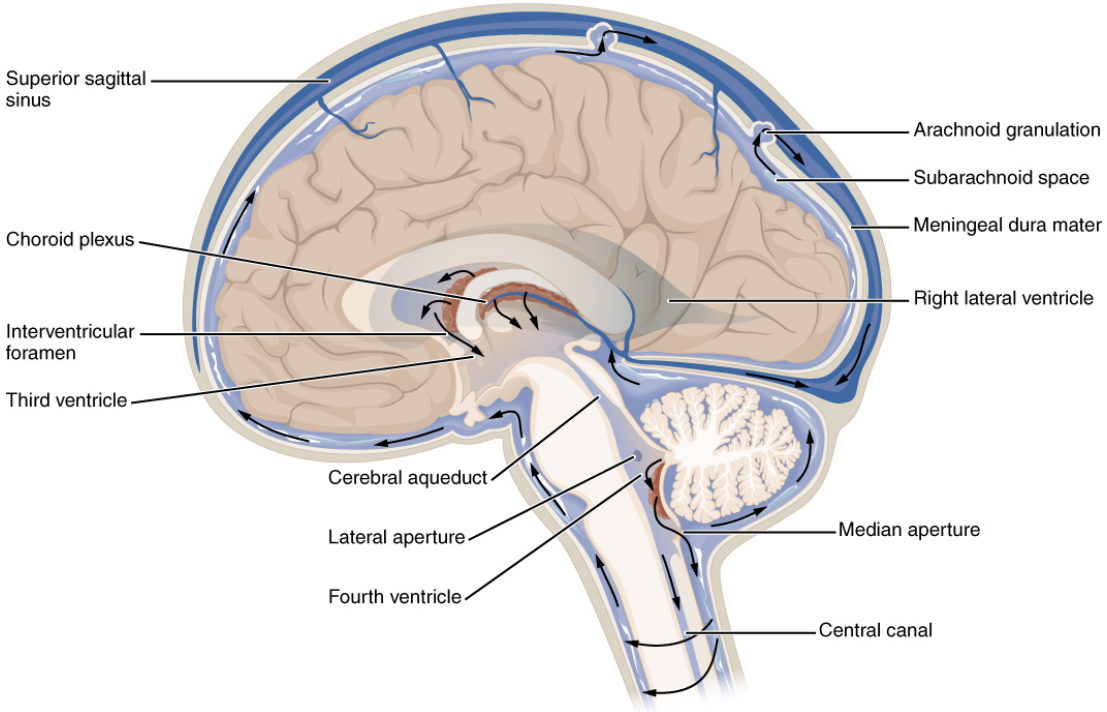


FIGURE 13.18 Cerebrospinal Fluid Circulation The choroid plexus in the four ventricles produce CSF, which is circulated through the ventricular system and then enters the subarachnoid space through the median and lateral apertures. The CSF is then reabsorbed into the blood at the arachnoid granulations, where the arachnoid membrane emerges into the dural sinuses.

As the telencephalon enlarges and grows into the cranial cavity, it is limited by the space within the skull. The telencephalon is the most anterior region of what was the neural tube, but cannot grow past the limit of the frontal bone of the skull. Because the cerebrum fits into this space, it takes on a C-shaped formation, through the frontal, parietal, occipital, and finally temporal regions. The space within the telencephalon is stretched into this same C-shape. The two ventricles are in the left and right sides, and were at one time referred to as the first and second ventricles. The interventricular foramina connect the frontal region of the lateral ventricles with the third ventricle.

The third ventricle is the space bounded by the medial walls of the hypothalamus and thalamus. The two thalami touch in the center in most brains as the massa intermedia, which is surrounded by the third ventricle. The cerebral aqueduct opens just inferior to the epithalamus and passes through the midbrain. The tectum and tegmentum of the midbrain are the roof and floor of the cerebral aqueduct, respectively. The aqueduct opens up into the fourth ventricle. The floor of the fourth ventricle is the dorsal surface of the pons and upper medulla (that gray matter making a continuation of the tegmentum of the midbrain). The fourth ventricle then narrows into the central canal of the spinal cord.

The ventricular system opens up to the subarachnoid space from the fourth ventricle. The single **median aperture** and the pair of **lateral apertures** connect to the subarachnoid space so that CSF can flow through the ventricles and around the outside of the CNS. Cerebrospinal fluid is produced within the ventricles by a type of specialized membrane called a **choroid plexus**. Ependymal cells (one of the types of glial cells described in the introduction to the nervous system) surround blood capillaries and filter the blood to make CSF. The fluid is a clear solution with a limited amount of the constituents of blood. It is essentially water, small molecules, and electrolytes. Oxygen and carbon dioxide are dissolved into the CSF, as they are in blood, and can diffuse between the fluid and the nervous tissue.

Cerebrospinal Fluid Circulation

The choroid plexuses are found in all four ventricles. Observed in dissection, they appear as soft, fuzzy structures that may still be pink, depending on how well the circulatory system is cleared in preparation of the tissue. The CSF is produced from components extracted from the blood, so its flow out of the ventricles is tied to the pulse of cardiovascular circulation.

From the lateral ventricles, the CSF flows into the third ventricle, where more CSF is produced, and then through the

Severe or limited memory loss can be the result of a temporal lobe stroke.

Related to strokes are transient ischemic attacks (TIAs), which can also be called "mini-strokes." These are events in which a physical blockage may be temporary, cutting off the blood supply and oxygen to a region, but not to the extent that it causes cell death in that region. While the neurons in that area are recovering from the event, neurological function may be lost. Function can return if the area is able to recover from the event.

Recovery from a stroke (or TIA) is strongly dependent on the speed of treatment. Often, the person who is present and notices something is wrong must then make a decision. The mnemonic **FAST** helps people remember what to look for when someone is dealing with sudden losses of neurological function. If someone complains of feeling "funny," check these things quickly: Look at the person's face. Do they have problems moving **F**ace muscles and making regular facial expressions? Ask the person to raise their **A**rms above the head. Can the person lift one arm but not the other? Has the person's **S**peech changed? Are they slurring words or having trouble saying things? If any of these things have happened, then it is **T**ime to call for help.

Sometimes, treatment with blood-thinning drugs can alleviate the problem, and recovery is possible. If the tissue is damaged, the amazing thing about the nervous system is that it is adaptable. With physical, occupational, and speech therapy, victims of strokes can recover, or more accurately relearn, functions.

13.4 The Peripheral Nervous System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structures found in the PNS
- Distinguish between somatic and autonomic structures, including the special peripheral structures of the enteric nervous system
- Name the twelve cranial nerves and explain the functions associated with each
- Describe the sensory and motor components of spinal nerves and the plexuses that they pass through

The PNS is not as contained as the CNS because it is defined as everything that is not the CNS. Some peripheral structures are incorporated into the other organs of the body. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures that are incorporated into other organs are features of the digestive system; these structures are known as the **enteric nervous system** and are a special subset of the PNS.

Ganglia

A ganglion is a group of neuron cell bodies in the periphery. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a **dorsal (posterior) root ganglion**. These ganglia are the cell bodies of neurons with axons that are sensory endings in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. The ganglion is an enlargement of the nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root (Figure 13.19). The cells of the dorsal root ganglion are unipolar cells, classifying them by shape. Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies.

cranial nerve ganglia are also unipolar in shape with associated satellite cells.

The other major category of ganglia are those of the autonomic nervous system, which is divided into the sympathetic and parasympathetic nervous systems. The **sympathetic chain ganglia** constitute a row of ganglia along the vertebral column that receive central input from the lateral horn of the thoracic and upper lumbar spinal cord. Superior to the chain ganglia are three **paravertebral ganglia** in the cervical region. Three other autonomic ganglia that are related to the sympathetic chain are the **prevertebral ganglia**, which are located outside of the chain but have similar functions. They are referred to as prevertebral because they are anterior to the vertebral column. The neurons of these autonomic ganglia are multipolar in shape, with dendrites radiating out around the cell body where synapses from the spinal cord neurons are made. The neurons of the chain, paravertebral, and prevertebral ganglia then project to organs in the head and neck, thoracic, abdominal, and pelvic cavities to regulate the sympathetic aspect of homeostatic mechanisms.

Another group of autonomic ganglia are the **terminal ganglia** that receive input from cranial nerves or sacral spinal nerves and are responsible for regulating the parasympathetic aspect of homeostatic mechanisms. These two sets of ganglia, sympathetic and parasympathetic, often project to the same organs—one input from the chain ganglia and one input from a terminal ganglion—to regulate the overall function of an organ. For example, the heart receives two inputs such as these; one increases heart rate, and the other decreases it. The terminal ganglia that receive input from cranial nerves are found in the head and neck, as well as the thoracic and upper abdominal cavities, whereas the terminal ganglia that receive sacral input are in the lower abdominal and pelvic cavities.

Terminal ganglia below the head and neck are often incorporated into the wall of the target organ as a **plexus**. A plexus, in a general sense, is a network of fibers or vessels. This can apply to nervous tissue (as in this instance) or structures containing blood vessels (such as a choroid plexus). For example, the **enteric plexus** is the extensive network of axons and neurons in the wall of the small and large intestines. The enteric plexus is actually part of the enteric nervous system, along with the **gastric plexuses** and the **esophageal plexus**. Though the enteric nervous system receives input originating from central neurons of the autonomic nervous system, it does not require CNS input to function. In fact, it operates independently to regulate the digestive system.

Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. The outer surface of a nerve is a surrounding layer of fibrous connective tissue called the **epineurium**. Within the nerve, axons are further bundled into **fascicles**, which are each surrounded by their own layer of fibrous connective tissue called **perineurium**. Finally, individual axons are surrounded by loose connective tissue called the **endoneurium** (Figure 13.21). These three layers are similar to the connective tissue sheaths for muscles. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord.

epineurium in greater detail (tissue source: simian). LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/nervetrunk) to explore the tissue sample in greater detail. With what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

Cranial Nerves

The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CNI through CNXII for "Cranial Nerve," using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves.

Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, "On Old Olympus' Towering Tops/A Finn And German Viewed Some Hops," in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in Table 13.3 along with a brief description of their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle). They are listed here with a brief explanation of each nerve (Figure 13.23).

The **olfactory nerve** and **optic nerve** are responsible for the sense of smell and vision, respectively. The **oculomotor nerve** is responsible for eye movements by controlling four of the **extraocular muscles**. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The **trochlear nerve** and the **abducens nerve** are both responsible for eye movement, but do so by controlling different extraocular muscles. The **trigeminal nerve** is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The **facial nerve** is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The **vestibulocochlear nerve** is responsible for the senses of hearing and balance. The **glossopharyngeal nerve** is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The **vagus nerve** is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The **spinal accessory nerve** is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The **hypoglossal nerve** is responsible for controlling the muscles of the lower throat and tongue.

Cranial Nerves

Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
On	I	Olfactory	Smell (S)	Olfactory bulb	Olfactory epithelium
Old	II	Optic	Vision (S)	Hypothalamus/ thalamus/midbrain	Retina (retinal ganglion cells)
Olympus'	III	Oculomotor	Eye movements (M)	Oculomotor nucleus	Extraocular muscles (other 4), levator palpebrae superioris, ciliary ganglion (autonomic)
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	Superior oblique muscle
Tops	V	Trigeminal	Sensory/ motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	Trigeminal
A	VI	Abducens	Eye movements (M)	Abducens nucleus	Lateral rectus muscle
Finn	VII	Facial	Motor – face, Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles, Geniculate ganglion, Pterygopalatine ganglion (autonomic)
And	VIII	Auditory (Vestibulocochlear)	Hearing/ balance (S)	Cochlear nucleus, Vestibular nucleus/ cerebellum	Spiral ganglion (hearing), Vestibular ganglion (balance)
German	IX	Glossopharyngeal	Motor – throat Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus	Pharyngeal muscles, Geniculate ganglion, Otic ganglion (autonomic)
Viewed	X	Vagus	Motor/ sensory – viscera (autonomic) (B)	Medulla	Terminal ganglia serving thoracic and upper abdominal organs (heart and small intestines)

TABLE 13.3

sensory neurons in the dorsal root ganglia that enter the spinal cord through the dorsal nerve root. Other fibers are the axons of motor neurons of the anterior horn of the spinal cord, which emerge in the ventral nerve root and send action potentials to cause skeletal muscles to contract in their target regions. For example, the radial nerve contains fibers of cutaneous sensation in the arm, as well as motor fibers that move muscles in the arm.

Spinal nerves of the thoracic region, T2 through T11, are not part of the plexuses but rather emerge and give rise to the **intercostal nerves** found between the ribs, which articulate with the vertebrae surrounding the spinal nerve.

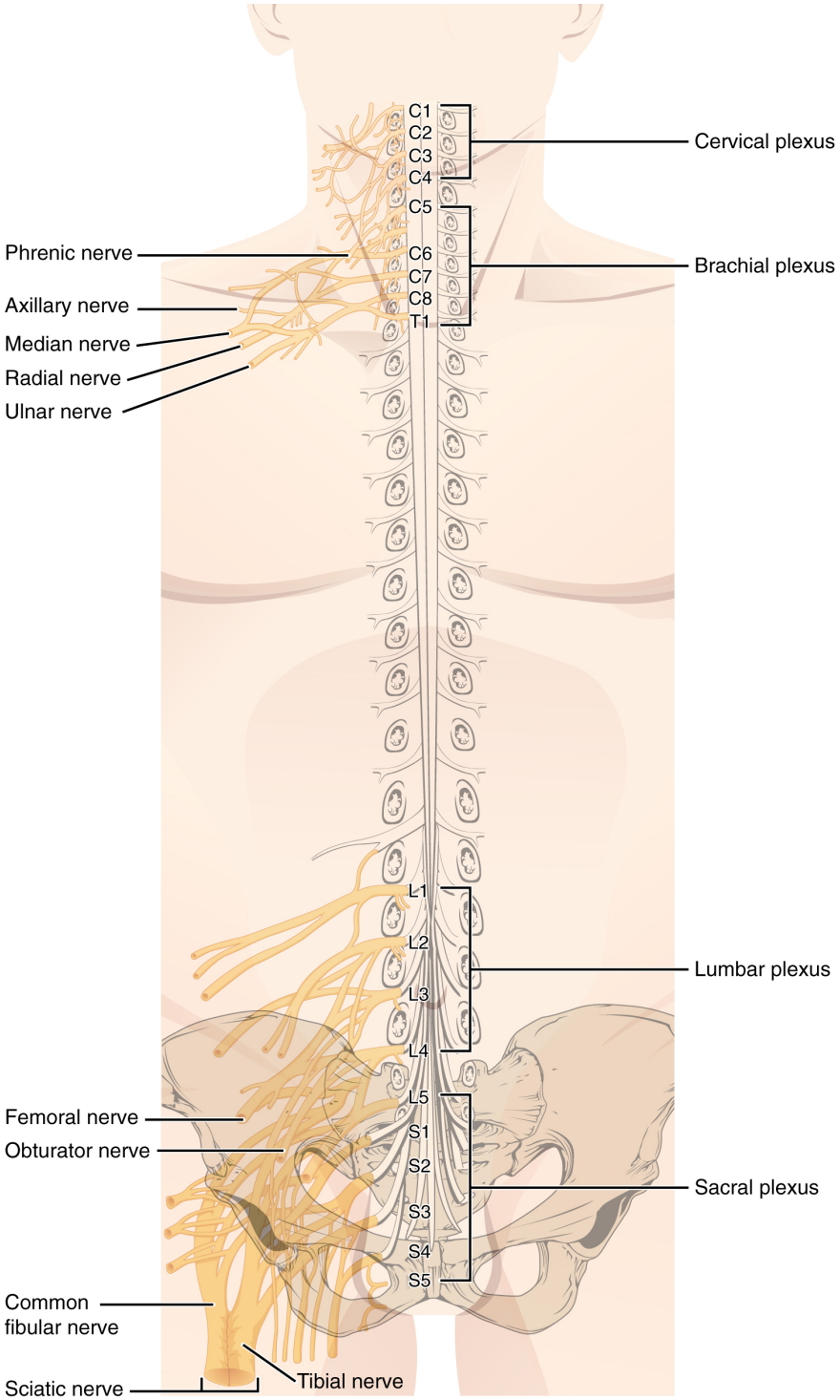


FIGURE 13.24 **Nerve Plexuses of the Body** There are four main nerve plexuses in the human body. The cervical plexus supplies nerves to the posterior head and neck, as well as to the diaphragm. The brachial plexus supplies nerves to the arm. The lumbar plexus supplies nerves to the anterior leg. The sacral plexus supplies nerves to the posterior leg.

Key Terms

abducens nerve sixth cranial nerve; responsible for contraction of one of the extraocular muscles

alar plate developmental region of the spinal cord that gives rise to the posterior horn of the gray matter

amygdala nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior

anterior column white matter between the anterior horns of the spinal cord composed of many different groups of axons of both ascending and descending tracts

anterior horn gray matter of the spinal cord containing multipolar motor neurons, sometimes referred to as the ventral horn

anterior median fissure deep midline feature of the anterior spinal cord, marking the separation between the right and left sides of the cord

anterior spinal artery blood vessel from the merged branches of the vertebral arteries that runs along the anterior surface of the spinal cord

arachnoid granulation outpocket of the arachnoid membrane into the dural sinuses that allows for reabsorption of CSF into the blood

arachnoid mater middle layer of the meninges named for the spider-web–like trabeculae that extend between it and the pia mater

arachnoid trabeculae filaments between the arachnoid and pia mater within the subarachnoid space

ascending tract central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain

axillary nerve systemic nerve of the arm that arises from the brachial plexus

basal forebrain nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease

basal nuclei nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases

basal plate developmental region of the spinal cord that gives rise to the lateral and anterior horns of gray matter

basilar artery blood vessel from the merged vertebral arteries that runs along the dorsal surface of the brain stem

brachial plexus nerve plexus associated with the lower cervical spinal nerves and first thoracic spinal nerve

brain stem region of the adult brain that includes the midbrain, pons, and medulla oblongata and develops from the mesencephalon, metencephalon, and myelencephalon of the embryonic brain

Broca's area region of the frontal lobe associated with the motor commands necessary for speech production and located only in the cerebral hemisphere responsible for language production, which is the left side in approximately 95 percent of the population

Brodmann's areas mapping of regions of the cerebral cortex based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s

carotid canal opening in the temporal bone through which the internal carotid artery enters the cranium

cauda equina bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail

caudate nucleus deep in the cerebrum that is part of the basal nuclei; along with the putamen, it is part of the striatum

central canal hollow space within the spinal cord that is the remnant of the center of the neural tube

central sulcus surface landmark of the cerebral cortex that marks the boundary between the frontal and parietal lobes

cephalic flexure curve in midbrain of the embryo that positions the forebrain ventrally

cerebellum region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord

cerebral aqueduct connection of the ventricular system between the third and fourth ventricles located in the midbrain

cerebral cortex outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci

cerebral hemisphere one half of the bilaterally symmetrical cerebrum

cerebrum region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion,

hypoglossal nerve twelfth cranial nerve; responsible for contraction of muscles of the tongue
hypothalamus major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis
indirect pathway connections within the basal nuclei from the striatum through the globus pallidus external segment and subthalamic nucleus to the globus pallidus internal segment/substantia nigra pars compacta that result in inhibition of the thalamus to decrease cortical control of movement
inferior colliculus half of the midbrain tectum that is part of the brain stem auditory pathway
inferior olive nucleus in the medulla that is involved in processing information related to motor control
intercostal nerve systemic nerve in the thoracic cavity that is found between two ribs
internal carotid artery branch from the common carotid artery that enters the cranium and supplies blood to the brain
interventricular foramina openings between the lateral ventricles and third ventricle allowing for the passage of CSF
jugular veins blood vessels that return "used" blood from the head and neck
kinesthesia general sensory perception of movement of the body
lateral apertures pair of openings from the fourth ventricle to the subarachnoid space on either side and between the medulla and cerebellum
lateral column white matter of the spinal cord between the posterior horn on one side and the axons from the anterior horn on the same side; composed of many different groups of axons, of both ascending and descending tracts, carrying motor commands to and from the brain
lateral horn region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system
lateral sulcus surface landmark of the cerebral cortex that marks the boundary between the temporal lobe and the frontal and parietal lobes
lateral ventricles portions of the ventricular system that are in the region of the cerebrum
limbic cortex collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system
limbic system structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation
longitudinal fissure large separation along the midline between the two cerebral hemispheres
lumbar plexus nerve plexus associated with the lumbar spinal nerves
lumbar puncture procedure used to withdraw CSF from the lower lumbar region of the vertebral column that avoids the risk of damaging CNS tissue because the spinal cord ends at the upper lumbar vertebrae
median aperture singular opening from the fourth ventricle into the subarachnoid space at the midline between the medulla and cerebellum
median nerve systemic nerve of the arm, located between the ulnar and radial nerves
meninges protective outer coverings of the CNS composed of connective tissue
mesencephalon primary vesicle of the embryonic brain that does not significantly change through the rest of embryonic development and becomes the midbrain
metencephalon secondary vesicle of the embryonic brain that develops into the pons and the cerebellum
midbrain middle region of the adult brain that develops from the mesencephalon
myelencephalon secondary vesicle of the embryonic brain that develops into the medulla
nerve plexus network of nerves without neuronal cell bodies included
neural crest tissue that detaches from the edges of the neural groove and migrates through the embryo to develop into peripheral structures of both nervous and non-nervous tissues
neural fold elevated edge of the neural groove
neural groove region of the neural plate that folds into the dorsal surface of the embryo and closes off to become the neural tube
neural plate thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue
neural tube precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium
neuraxis central axis to the nervous system, from the posterior to anterior ends of the neural tube; the inferior tip of the spinal cord to the anterior surface of the cerebrum
occipital lobe region of the cerebral cortex directly beneath the occipital bone of the cranium
occipital sinuses dural sinuses along the edge of the occipital lobes of the cerebrum
oculomotor nerve third cranial nerve; responsible for contraction of four of the extraocular muscles, the muscle in the upper eyelid, and pupillary

mater and pia mater that contains CSF and the fibrous connections of the arachnoid trabeculae

subcortical nucleus all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

substantia nigra pars compacta nuclei within the basal nuclei that release dopamine to modulate the function of the striatum; part of the motor pathway

substantia nigra pars reticulata nuclei within the basal nuclei that serve as an output center of the nuclei; part of the motor pathway

subthalamus nucleus within the basal nuclei that is part of the indirect pathway

sulcus groove formed by convolutions in the surface of the cerebral cortex

superior colliculus half of the midbrain tectum that is responsible for aligning visual, auditory, and somatosensory spatial perceptions

superior sagittal sinus dural sinus that runs along the top of the longitudinal fissure and drains blood from the majority of the outer cerebrum

sympathetic chain ganglia autonomic ganglia in a chain along the anterolateral aspect of the vertebral column that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

systemic nerve nerve in the periphery distal to a nerve plexus or spinal nerve

tectum region of the midbrain, thought of as the roof of the cerebral aqueduct, which is subdivided into the inferior and superior colliculi

tegmentum region of the midbrain, thought of as the floor of the cerebral aqueduct, which continues into the pons and medulla as the floor of the fourth ventricle

telencephalon secondary vesicle of the embryonic brain that develops into the cerebrum

temporal lobe region of the cerebral cortex directly beneath the temporal bone of the cranium

terminal ganglion autonomic ganglia that are near or within the walls of organs that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

thalamus major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain, spinal cord, and periphery

third ventricle portion of the ventricular system that is in the region of the diencephalon

tibial nerve systemic nerve of the posterior leg that begins as part of the sciatic nerve

transverse sinuses dural sinuses that drain along either side of the occipital–cerebellar space

trigeminal ganglion sensory ganglion that contributes sensory fibers to the trigeminal nerve

trigeminal nerve fifth cranial nerve; responsible for cutaneous sensation of the face and contraction of the muscles of mastication

trochlear nerve fourth cranial nerve; responsible for contraction of one of the extraocular muscles

ulnar nerve systemic nerve of the arm located close to the ulna, a bone of the forearm

vagus nerve tenth cranial nerve; responsible for the autonomic control of organs in the thoracic and upper abdominal cavities

ventral (anterior) nerve root axons emerging from the anterior or lateral horns of the spinal cord

ventricles remnants of the hollow center of the neural tube that are spaces for cerebrospinal fluid to circulate through the brain

vertebral arteries arteries that ascend along either side of the vertebral column through the transverse foramina of the cervical vertebrae and enter the cranium through the foramen magnum

vestibulocochlear nerve eighth cranial nerve; responsible for the sensations of hearing and balance

Chapter Review

13.1 The Embryologic Perspective

The development of the nervous system starts early in embryonic development. The outer layer of the embryo, the ectoderm, gives rise to the skin and the nervous system. A specialized region of this layer, the neuroectoderm, becomes a groove that folds in and becomes the neural tube beneath the dorsal surface of the embryo. The anterior end of the neural tube develops into the brain, and the posterior region becomes the spinal cord. Tissues at the edges of the neural groove, when it closes off, are called the neural crest and migrate through the embryo to give rise to PNS structures as well as some non-nervous tissues.

The brain develops from this early tube structure and gives rise to specific regions of the adult brain. As the neural tube grows and differentiates, it enlarges into three vesicles that correspond to the forebrain, midbrain, and hindbrain regions of the adult brain. Later in development, two of these three vesicles differentiate further, resulting in five vesicles. Those five vesicles can be aligned with the four major regions of the adult brain. The cerebrum is formed directly from the telencephalon. The diencephalon is the only region that keeps its embryonic name. The

(ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. Ganglia are of two types, sensory or autonomic. Sensory ganglia contain unipolar sensory neurons and are found on the dorsal root of all spinal nerves as well as associated with many of the cranial nerves. Autonomic ganglia are in the sympathetic chain, the associated paravertebral or prevertebral ganglia, or in terminal ganglia near or within the organs controlled by the autonomic nervous system.

Nerves are classified as cranial nerves or spinal nerves on the basis of their connection to the brain or spinal cord, respectively. The twelve cranial nerves can be strictly sensory in function, strictly motor in function, or a combination of the two functions. Sensory fibers are axons of sensory ganglia that carry sensory information into the brain and target sensory nuclei. Motor fibers are axons of motor neurons in motor nuclei of the brain stem and target skeletal muscles of the head and neck. Spinal nerves are all mixed nerves with both sensory and motor fibers. Spinal nerves emerge from the spinal cord and reorganize through plexuses, which then give rise to systemic nerves. Thoracic spinal nerves are not part of any plexus, but give rise to the intercostal nerves directly.

Interactive Link Questions

1. Watch this animation (http://openstax.org/l/braindevel) to examine the development of the brain, starting with the neural tube. As the anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?
2. Watch this video (http://openstax.org/l/whitematter) to learn about the white matter in the cerebrum that develops during childhood and adolescence. This is a composite of MRI images taken of the brains of people from 5 years of age through 20 years of age, demonstrating how the cerebrum changes. As the color changes to blue, the ratio of gray matter to white matter changes. The caption for the video describes it as “less gray matter,” which is another way of saying “more white matter.” If the brain does not finish developing until approximately 20 years of age, can teenagers be held responsible for behaving badly?
3. Watch this video (http://openstax.org/l/basalnuclei1) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?
4. Watch this video (http://openstax.org/l/basalnuclei2) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?
5. Watch this video (http://openstax.org/l/graymatter) to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

17. Which structure is associated with the embryologic development of the peripheral nervous system?
a. neural crest
b. neuraxis
c. rhombencephalon
d. neural tube

18. Which lobe of the cerebral cortex is responsible for generating motor commands?
a. temporal
b. parietal
c. occipital
d. frontal

19. What region of the diencephalon coordinates homeostasis?
a. thalamus
b. epithalamus
c. hypothalamus
d. subthalamus

20. What level of the brain stem is the major input to the cerebellum?
a. midbrain
b. pons
c. medulla
d. spinal cord

21. What region of the spinal cord contains motor neurons that direct the movement of skeletal muscles?
a. anterior horn
b. posterior horn
c. lateral horn
d. alar plate

22. Brodmann's areas map different regions of the _____ to particular functions.
a. cerebellum
b. cerebral cortex
c. basal forebrain
d. corpus callosum

23. What blood vessel enters the cranium to supply the brain with fresh, oxygenated blood?
a. common carotid artery
b. jugular vein
c. internal carotid artery
d. aorta

24. Which layer of the meninges surrounds and supports the sinuses that form the route through which blood drains from the CNS?
a. dura mater
b. arachnoid mater
c. subarachnoid
d. pia mater

25. What type of glial cell is responsible for filtering blood to produce CSF at the choroid plexus?
a. ependymal cell
b. astrocyte
c. oligodendrocyte
d. Schwann cell

26. Which portion of the ventricular system is found within the diencephalon?
a. lateral ventricles
b. third ventricle
c. cerebral aqueduct
d. fourth ventricle

27. What condition causes a stroke?
a. inflammation of meninges
b. lumbar puncture
c. infection of cerebral spinal fluid
d. disruption of blood to the brain

28. What type of ganglion contains neurons that control homeostatic mechanisms of the body?
a. sensory ganglion
b. dorsal root ganglion
c. autonomic ganglion
d. cranial nerve ganglion

29. Which ganglion is responsible for cutaneous sensations of the face?
a. otic ganglion
b. vestibular ganglion
c. geniculate ganglion
d. trigeminal ganglion

30. What is the name for a bundle of axons within a nerve?
a. fascicle
b. tract
c. nerve root
d. epineurium

31. Which cranial nerve does not control functions in the head and neck?
a. olfactory
b. trochlear
c. glossopharyngeal
d. vagus

collateral branch of the sensory axon would inhibit another ventral horn motor neuron so that the triceps brachii do not contract and slow the withdrawal down. The cross extensor reflex provides a counterbalancing movement on the other side of the body, which requires another collateral of the sensory axon to activate contraction of the extensor muscles in the contralateral limb.

A more complex example of somatic function is conscious muscle movement. For example, reading of this text starts with visual sensory input to the retina, which then projects to the thalamus, and on to the cerebral cortex. A sequence of regions of the cerebral cortex process the visual information, starting in the primary visual cortex of the occipital lobe, and resulting in the conscious perception of these letters. Subsequent cognitive processing results in understanding of the content. As you continue reading, regions of the cerebral cortex in the frontal lobe plan how to move the eyes to follow the lines of text. The output from the cortex causes activity in motor neurons in the brain stem that cause movement of the extraocular muscles through the third, fourth, and sixth cranial nerves. This example also includes sensory input (the retinal projection to the thalamus), central processing (the thalamus and subsequent cortical activity), and motor output (activation of neurons in the brain stem that lead to coordinated contraction of extraocular muscles).

14.1 Sensory Perception

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe different types of sensory receptors
- Describe the structures responsible for the special senses of taste, smell, hearing, balance, and vision
- Distinguish how different tastes are transduced
- Describe the means of mechanoreception for hearing and balance
- List the supporting structures around the eye and describe the structure of the eyeball
- Describe the processes of phototransduction

A major role of sensory receptors is to help us learn about the environment around us, or about the state of our internal environment. Stimuli from varying sources, and of different types, are received and changed into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response.

Describing sensory function with the term sensation or perception is a deliberate distinction. Sensation is the activation of sensory receptor cells at the level of the stimulus. Perception is the central processing of sensory stimuli into a meaningful pattern. Perception is dependent on sensation, but not all sensations are perceived. Receptors are the cells or structures that detect sensations. A receptor cell is changed directly by a stimulus. A transmembrane protein receptor is a protein in the cell membrane that mediates a physiological change in a neuron, most often through the opening of ion channels or changes in the cell signaling processes. Transmembrane receptors are activated by chemicals called ligands. For example, a molecule in food can serve as a ligand for taste receptors. Other transmembrane proteins, which are not accurately called receptors, are sensitive to mechanical or thermal changes. Physical changes in these proteins increase ion flow across the membrane, and can generate an action potential or a graded potential in the sensory neurons.

Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the **transduction** of stimuli, or how the mechanical stimulus, light, or chemical changed the cell membrane potential.

Structural Receptor Types

The cells that interpret information about the environment can be either (1) a neuron that has a **free nerve ending**,

the basis of the type of mechanoreceptors that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors.

Within the realm of physiology, senses can be classified as either general or specific. A **general sense** is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to **proprioception** (body movement) and **kinesthesia** (body movement), or to a **visceral sense**, which is most important to autonomic functions. A **special sense** is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose.

Each of the senses is referred to as a **sensory modality**. Modality refers to the way that information is encoded, which is similar to the idea of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors.

Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or **submodalities**, of the larger sense. An individual sensory modality represents the sensation of a specific type of stimulus. For example, the general sense of touch, which is known as **somatosensation**, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

Gustation (Taste)

Only a few recognized submodalities exist within the sense of taste, or **gustation**. Until recently, only four tastes were recognized: sweet, salty, sour, and bitter. Research at the turn of the 20th century led to recognition of the fifth taste, umami, during the mid-1980s. **Umami** is a Japanese word that means “delicious taste,” and is often translated to mean savory. Very recent research has suggested that there may also be a sixth taste for fats, or lipids.

Gustation is the special sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Raised bumps called **papillae** (singular = papilla) contain the structures for gustatory transduction. There are four types of papillae, based on their appearance (Figure 14.3): circumvallate, foliate, filiform, and fungiform. Within the structure of the papillae are **taste buds** that contain specialized **gustatory receptor cells** for the transduction of taste stimuli. These receptor cells are sensitive to the chemicals contained within foods that are ingested, and they release neurotransmitters based on the amount of the chemical in the food. Neurotransmitters from the gustatory cells can activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves.

protein activation. The specific response depends on which molecule is binding to the receptor.

One major group of bitter-tasting molecules are alkaloids. **Alkaloids** are nitrogen containing molecules that are commonly found in bitter-tasting plant products, such as coffee, hops (in beer), tannins (in wine), tea, and aspirin. By containing toxic alkaloids, the plant is less susceptible to microbe infection and less attractive to herbivores.

Therefore, the function of bitter taste may primarily be related to stimulating the gag reflex to avoid ingesting poisons. Because of this, many bitter foods that are normally ingested are often combined with a sweet component to make them more palatable (cream and sugar in coffee, for example). The highest concentration of bitter receptors appear to be in the posterior tongue, where a gag reflex could still spit out poisonous food.

The taste known as umami is often referred to as the savory taste. Like sweet and bitter, it is based on the activation of G protein–coupled receptors by a specific molecule. The molecule that activates this receptor is the amino acid L-glutamate. Therefore, the umami flavor is often perceived while eating protein-rich foods. Not surprisingly, dishes that contain meat are often described as savory.

Once the gustatory cells are activated by the taste molecules, they release neurotransmitters onto the dendrites of sensory neurons. These neurons are part of the facial and glossopharyngeal cranial nerves, as well as a component within the vagus nerve dedicated to the gag reflex. The facial nerve connects to taste buds in the anterior third of the tongue. The glossopharyngeal nerve connects to taste buds in the posterior two thirds of the tongue. The vagus nerve connects to taste buds in the extreme posterior of the tongue, verging on the pharynx, which are more sensitive to noxious stimuli such as bitterness.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/DanielleReed) to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, Pennsylvania, who became interested in science at an early age because of her sensory experiences. She recognized that her sense of taste was unique compared with other people she knew. Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is able to visualize and count papillae on the surface of the tongue. People fall into two groups known as “tasters” and “non-tasters” based on the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?

Olfaction (Smell)

Like taste, the sense of smell, or **olfaction**, is also responsive to chemical stimuli. The olfactory receptor neurons are located in a small region within the superior nasal cavity (Figure 14.4). This region is referred to as the **olfactory epithelium** and contains bipolar sensory neurons. Each **olfactory sensory neuron** has dendrites that extend from the apical surface of the epithelium into the mucus lining the cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory epithelial region and dissolve into the mucus. These **odorant molecules** bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory dendrites. The odorant–protein complex binds to a receptor protein within the cell membrane of an olfactory dendrite. These receptors are G protein–coupled, and will produce a graded membrane potential in the olfactory neurons.

The axon of an olfactory neuron extends from the basal surface of the epithelium, through an olfactory foramen in the cribriform plate of the ethmoid bone, and into the brain. The group of axons called the olfactory tract connect to the **olfactory bulb** on the ventral surface of the frontal lobe. From there, the axons split to travel to several brain regions. Some travel to the cerebrum, specifically to the primary olfactory cortex that is located in the inferior and medial areas of the temporal lobe. Others project to structures within the limbic system and hypothalamus, where smells become associated with long-term memory and emotional responses. This is how certain smells trigger emotional memories, such as the smell of food associated with one’s birthplace. Smell is the one sensory modality that does not synapse in the thalamus before connecting to the cerebral cortex. This intimate connection between the olfactory system and the cerebral cortex is one reason why smell can be a potent trigger of memories and emotion.

of mild depression, because the loss of enjoyment of food may lead to a general sense of despair.

The ability of olfactory neurons to replace themselves decreases with age, leading to age-related anosmia. This explains why some elderly people salt their food more than younger people do. However, this increased sodium intake can increase blood volume and blood pressure, increasing the risk of cardiovascular diseases in the elderly.

Audition (Hearing)

Hearing, or **audition**, is the transduction of sound waves into a neural signal that is made possible by the structures of the ear (Figure 14.5). The large, fleshy structure on the lateral aspect of the head is known as the **auricle**. Some sources will also refer to this structure as the pinna, though that term is more appropriate for a structure that can be moved, such as the external ear of a cat. The C-shaped curves of the auricle direct sound waves toward the auditory canal. The canal enters the skull through the external auditory meatus of the temporal bone. At the end of the auditory canal is the **tympanic membrane**, or ear drum, which vibrates after it is struck by sound waves. The auricle, ear canal, and tympanic membrane are often referred to as the **external ear**. The **middle ear** consists of a space spanned by three small bones called the **ossicles**. The three ossicles are the **malleus**, **incus**, and **stapes**, which are Latin names that roughly translate to hammer, anvil, and stirrup. The malleus is attached to the tympanic membrane and articulates with the incus. The incus, in turn, articulates with the stapes. The stapes is then attached to the **inner ear**, where the sound waves will be transduced into a neural signal. The middle ear is connected to the pharynx through the Eustachian tube, which helps equilibrate air pressure across the tympanic membrane. The tube is normally closed but will pop open when the muscles of the pharynx contract during swallowing or yawning.

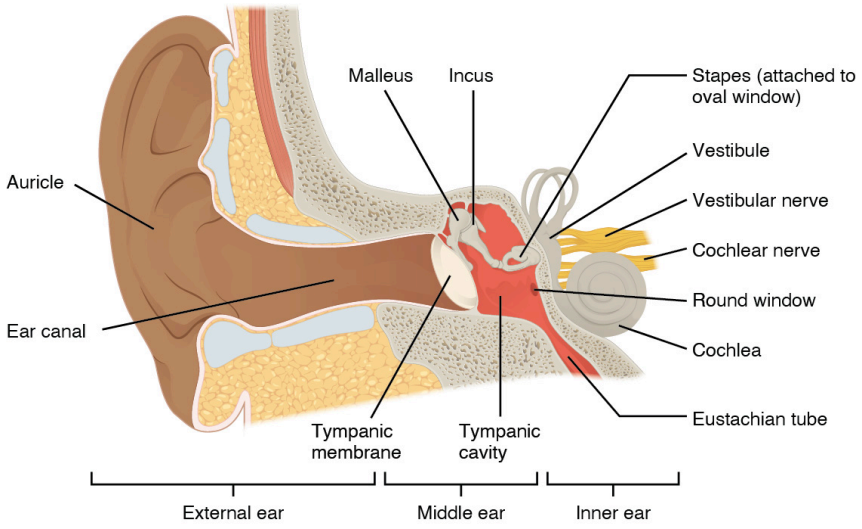


FIGURE 14.5 Structures of the Ear The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively.

The inner ear is often described as a bony labyrinth, as it is composed of a series of canals embedded within the temporal bone. It has two separate regions, the **cochlea** and the **vestibule**, which are responsible for hearing and balance, respectively. The neural signals from these two regions are relayed to the brain stem through separate fiber bundles. However, these two distinct bundles travel together from the inner ear to the brain stem as the vestibulocochlear nerve. Sound is transduced into neural signals within the cochlear region of the inner ear, which contains the sensory neurons of the **spiral ganglia**. These ganglia are located within the spiral-shaped cochlea of the inner ear. The cochlea is attached to the stapes through the **oval window**.

The oval window is located at the beginning of a fluid-filled tube within the cochlea called the **scala vestibuli**. The scala vestibuli extends from the oval window, travelling above the **cochlear duct**, which is the central cavity of the cochlea that contains the sound-transducing neurons. At the uppermost tip of the cochlea, the scala vestibuli curves over the top of the cochlear duct. The fluid-filled tube, now called the **scala tympani**, returns to the base of the cochlea, this time travelling under the cochlear duct. The scala tympani ends at the **round window**, which is

vestibuli lie on either side of the cochlear duct. The organ of Corti, containing the mechanoreceptor hair cells, is adjacent to the scala tympani, where it sits atop the basilar membrane.

The organs of Corti contain **hair cells**, which are named for the hair-like **stereocilia** extending from the cell's apical surfaces (Figure 14.8). The stereocilia are an array of microvilli-like structures arranged from tallest to shortest. Protein fibers tether adjacent hairs together within each array, such that the array will bend in response to movements of the basilar membrane. The stereocilia extend up from the hair cells to the overlying **tectorial membrane**, which is attached medially to the organ of Corti. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the tallest member of each array. When the stereocilia bend toward the tallest member of their array, tension in the protein tethers opens ion channels in the hair cell membrane. This will depolarize the hair cell membrane, triggering nerve impulses that travel down the afferent nerve fibers attached to the hair cells. When the stereocilia bend toward the shortest member of their array, the tension on the tethers slackens and the ion channels close. When no sound is present, and the stereocilia are standing straight, a small amount of tension still exists on the tethers, keeping the membrane potential of the hair cell slightly depolarized.

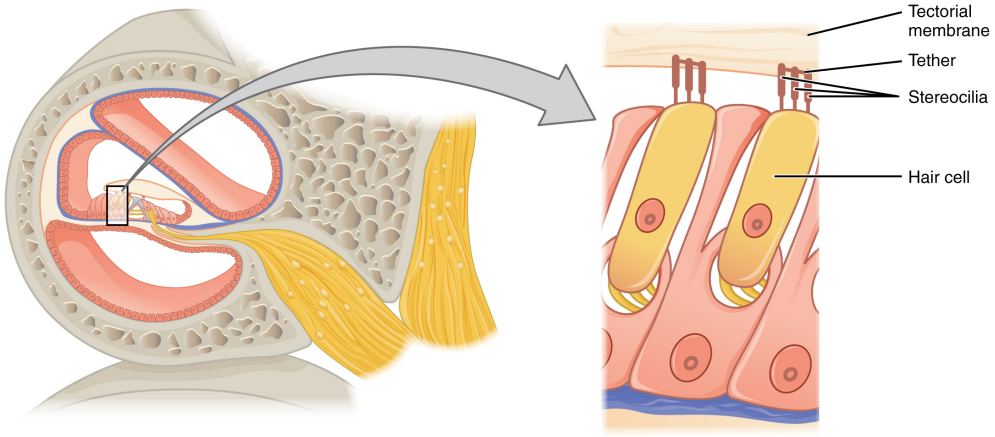


FIGURE 14.8 Hair Cell The hair cell is a mechanoreceptor with an array of stereocilia emerging from its apical surface. The stereocilia are tethered together by proteins that open ion channels when the array is bent toward the tallest member of their array, and closed when the array is bent toward the shortest member of their array.

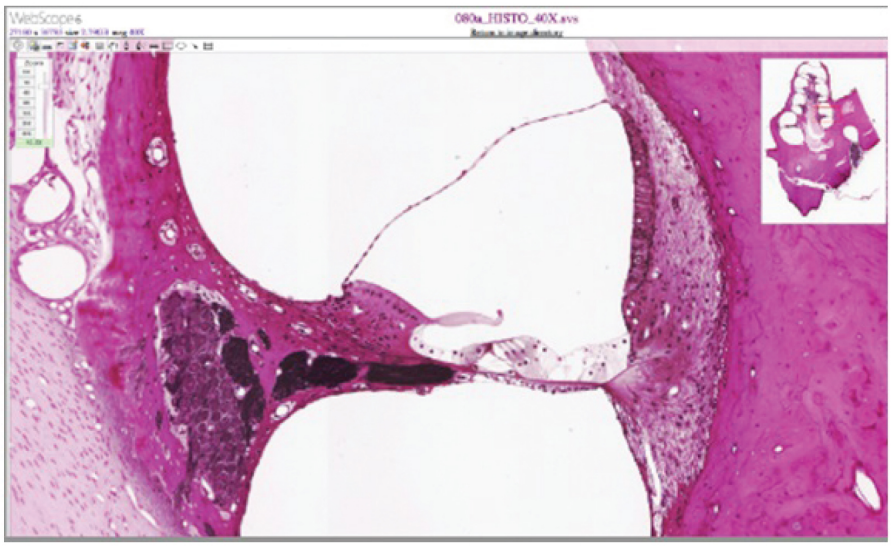


FIGURE 14.9 Cochlea and Organ of Corti LM × 412. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/cochleaMG) to explore the tissue sample in greater detail. The basilar membrane is the thin membrane that extends from the central core of the cochlea to the edge.

Equilibrium (Balance)

Along with audition, the inner ear is responsible for encoding information about **equilibrium**, the sense of balance. A similar mechanoreceptor—a hair cell with stereocilia—senses head position, head movement, and whether our bodies are in motion. These cells are located within the vestibule of the inner ear. Head position is sensed by the **utricle** and **saccule**, whereas head movement is sensed by the **semicircular canals**. The neural signals generated in the **vestibular ganglion** are transmitted through the vestibulocochlear nerve to the brain stem and cerebellum.

The utricle and saccule are both largely composed of **macula** tissue (plural = maculae). The macula is composed of hair cells surrounded by support cells. The stereocilia of the hair cells extend into a viscous gel called the **otolithic membrane** (Figure 14.11). On top of the otolithic membrane is a layer of calcium carbonate crystals, called otoliths. The otoliths essentially make the otolithic membrane top-heavy. The otolithic membrane moves separately from the macula in response to head movements. Tilting the head causes the otolithic membrane to slide over the macula in the direction of gravity. The moving otolithic membrane, in turn, bends the sterocilia, causing some hair cells to depolarize as others hyperpolarize. The exact position of the head is interpreted by the brain based on the pattern of hair-cell depolarization.

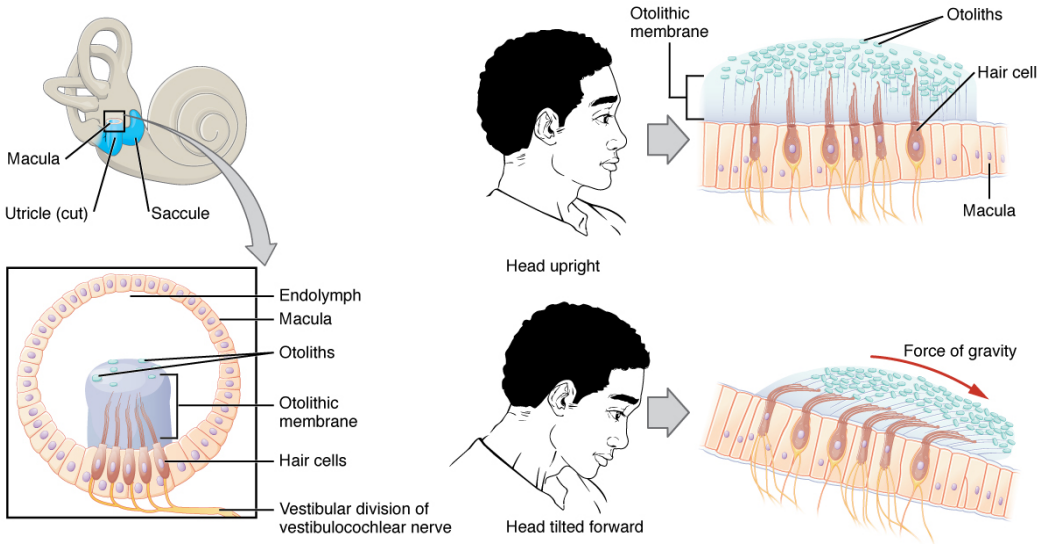


FIGURE 14.11 Linear Acceleration Coding by Maculae The maculae are specialized for sensing linear acceleration, such as when gravity acts on the tilting head, or if the head starts moving in a straight line. The difference in inertia between the hair cell stereocilia and the otolithic membrane in which they are embedded leads to a shearing force that causes the stereocilia to bend in the direction of that linear acceleration.

The semicircular canals are three ring-like extensions of the vestibule. One is oriented in the horizontal plane, whereas the other two are oriented in the vertical plane. The anterior and posterior vertical canals are oriented at approximately 45 degrees relative to the sagittal plane (Figure 14.12). The base of each semicircular canal, where it meets with the vestibule, connects to an enlarged region known as the **ampulla**. The ampulla contains the hair cells that respond to rotational movement, such as turning the head while saying “no.” The stereocilia of these hair cells extend into the **cupula**, a membrane that attaches to the top of the ampulla. As the head rotates in a plane parallel to the semicircular canal, the fluid lags, deflecting the cupula in the direction opposite to the head movement. The semicircular canals contain several ampullae, with some oriented horizontally and others oriented vertically. By comparing the relative movements of both the horizontal and vertical ampullae, the vestibular system can detect the direction of most head movements within three-dimensional (3-D) space.

Golgi tendon organs similarly transduce the stretch levels of tendons. Bulbous corpuscles are also present in joint capsules, where they measure stretch in the components of the skeletal system within the joint. The types of nerve endings, their locations, and the stimuli they transduce are presented in Table 14.1.

Mechanoreceptors of Somatosensation

Name	Historical (eponymous) name	Location(s)	Stimuli
Free nerve endings	*	Dermis, cornea, tongue, joint capsules, visceral organs	Pain, temperature, mechanical deformation
Mechanoreceptors	Merkel's discs	Epidermal–dermal junction, mucosal membranes	Low frequency vibration (5–15 Hz)
Bulbous corpuscle	Ruffini's corpuscle	Dermis, joint capsules	Stretch
Tactile corpuscle	Meissner's corpuscle	Papillary dermis, especially in the fingertips and lips	Light touch, vibrations below 50 Hz
Lamellated corpuscle	Pacinian corpuscle	Deep dermis, subcutaneous tissue	Deep pressure, high-frequency vibration (around 250 Hz)
Hair follicle plexus	*	Wrapped around hair follicles in the dermis	Movement of hair
Muscle spindle	*	In line with skeletal muscle fibers	Muscle contraction and stretch
Tendon stretch organ	Golgi tendon organ	In line with tendons	Stretch of tendons

TABLE 14.1 *No corresponding eponymous name.

Vision

Vision is the special sense of sight that is based on the transduction of light stimuli received through the eyes. The eyes are located within either orbit in the skull. The bony orbits surround the eyeballs, protecting them and anchoring the soft tissues of the eye (Figure 14.13). The eyelids, with lashes at their leading edges, help to protect the eye from abrasions by blocking particles that may land on the surface of the eye. The inner surface of each lid is a thin membrane known as the **palpebral conjunctiva**. The conjunctiva extends over the white areas of the eye (the sclera), connecting the eyelids to the eyeball. Tears are produced by the **lacrimal gland**, located just inside the orbit, superior and lateral to the eyeball. Tears produced by this gland flow through the **lacrimal duct** to the medial corner of the eye, where the tears flow over the conjunctiva, washing away foreign particles.

The eye itself is a hollow sphere composed of three layers of tissue. The outermost layer is the **fibrous tunic**, which includes the white **sclera** and clear **cornea**. The sclera accounts for five sixths of the surface of the eye, most of which is not visible, though humans are unique compared with many other species in having so much of the "white of the eye" visible (Figure 14.15). The transparent cornea covers the anterior tip of the eye and allows light to enter the eye. The middle layer of the eye is the **vascular tunic**, which is mostly composed of the choroid, ciliary body, and iris. The **choroid** is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the **ciliary body**, a muscular structure that is attached to the **lens** by suspensory ligaments, or **zonule fibers**. These two structures bend the lens, allowing it to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the **iris**—the colored part of the eye. The iris is a smooth muscle that opens or closes the **pupil**, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the **neural tunic**, or **retina**, which contains the nervous tissue responsible for photoreception.

The eye is also divided into two cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the **aqueous humor**. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the **vitreous humor**.

The retina is composed of several layers and contains specialized cells for the initial processing of visual stimuli. The photoreceptors (rods and cones) change their membrane potential when stimulated by light energy. The change in membrane potential alters the amount of neurotransmitter that the photoreceptor cells release onto **bipolar cells** in the **outer synaptic layer**. It is the bipolar cell in the retina that connects a photoreceptor to a **retinal ganglion cell (RGC)** in the **inner synaptic layer**. There, **amacrine cells** additionally contribute to retinal processing before an action potential is produced by the RGC. The axons of RGCs, which lie at the innermost layer of the retina, collect at the **optic disc** and leave the eye as the **optic nerve** (see Figure 14.15). Because these axons pass through the retina, there are no photoreceptors at the very back of the eye, where the optic nerve begins. This creates a "blind spot" in the retina, and a corresponding blind spot in our visual field.

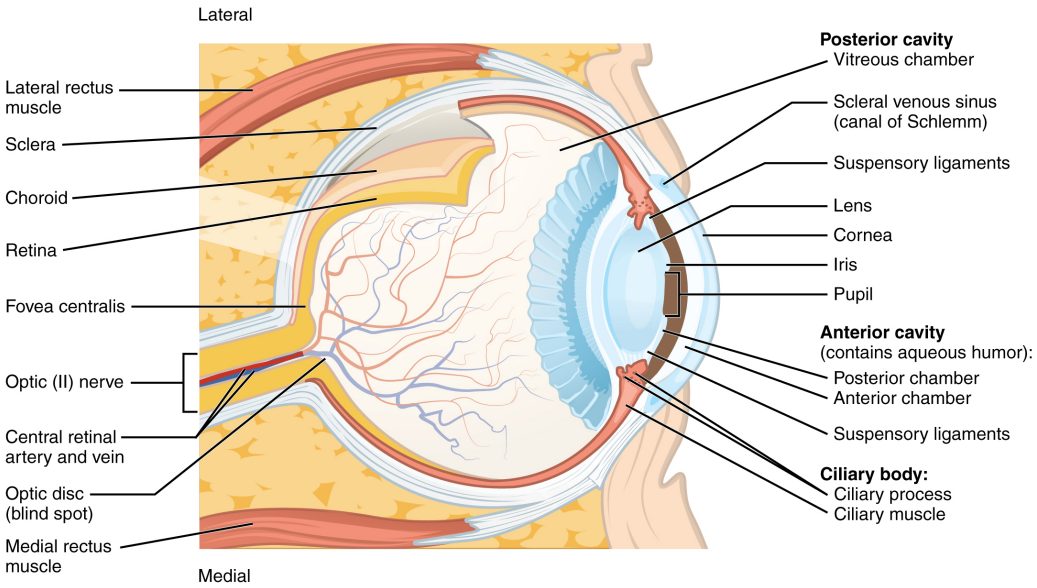


FIGURE 14.15 Structure of the Eye The sphere of the eye can be divided into anterior and posterior chambers. The wall of the eye is composed of three layers: the fibrous tunic, vascular tunic, and neural tunic. Within the neural tunic is the retina, with three layers of cells and two synaptic layers in between. The center of the retina has a small indentation known as the fovea.

Note that the photoreceptors in the retina (rods and cones) are located behind the axons, RGCs, bipolar cells, and retinal blood vessels. A significant amount of light is absorbed by these structures before the light reaches the photoreceptor cells. However, at the exact center of the retina is a small area known as the **fovea**. At the fovea, the retina lacks the supporting cells and blood vessels, and only contains photoreceptors. Therefore, **visual acuity**, or the sharpness of vision, is greatest at the fovea. This is because the fovea is where the least amount of incoming light is absorbed by other retinal structures (see Figure 14.15). As one moves in either direction from this central

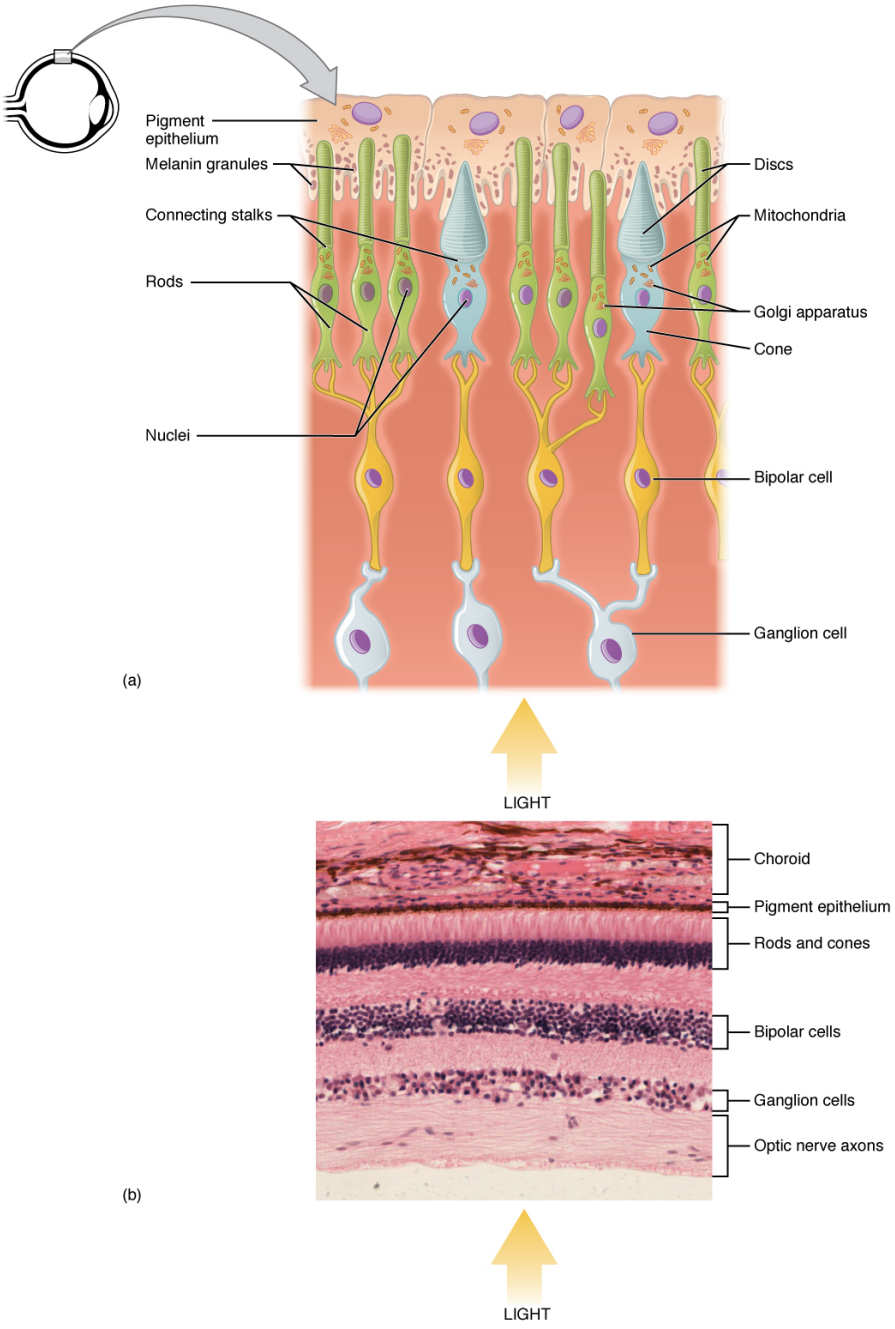


FIGURE 14.16 Photoreceptor (a) All photoreceptors have inner segments containing the nucleus and other important organelles and outer segments with membrane arrays containing the photosensitive opsin molecules. Rod outer segments are long columnar shapes with stacks of membrane-bound discs that contain the rhodopsin pigment. Cone outer segments are short, tapered shapes with folds of membrane in place of the discs in the rods. (b) Tissue of the retina shows a dense layer of nuclei of the rods and cones. LM × 800. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

At the molecular level, visual stimuli cause changes in the photopigment molecule that lead to changes in membrane potential of the photoreceptor cell. A single unit of light is called a **photon**, which is described in physics as a packet of energy with properties of both a particle and a wave. The energy of a photon is represented by its wavelength, with each wavelength of visible light corresponding to a particular color. Visible light is electromagnetic radiation with a wavelength between 380 and 720 nm. Wavelengths of electromagnetic radiation longer than 720 nm fall into the infrared range, whereas wavelengths shorter than 380 nm fall into the ultraviolet range. Light with a wavelength of 380 nm is blue whereas light with a wavelength of 720 nm is dark red. All other colors fall between red and blue at various points along the wavelength scale.

Opsin pigments are actually transmembrane proteins that contain a cofactor known as **retinal**. Retinal is a

The three types of cone opsins, being sensitive to different wavelengths of light, provide us with color vision. By comparing the activity of the three different cones, the brain can extract color information from visual stimuli. For example, a bright blue light that has a wavelength of approximately 450 nm would activate the "red" cones minimally, the "green" cones marginally, and the "blue" cones predominantly. The relative activation of the three different cones is calculated by the brain, which perceives the color as blue. However, cones cannot react to low-intensity light, and rods do not sense the color of light. Therefore, our low-light vision is—in essence—in grayscale. In other words, in a dark room, everything appears as a shade of gray. If you think that you can see colors in the dark, it is most likely because your brain knows what color something is and is relying on that memory.

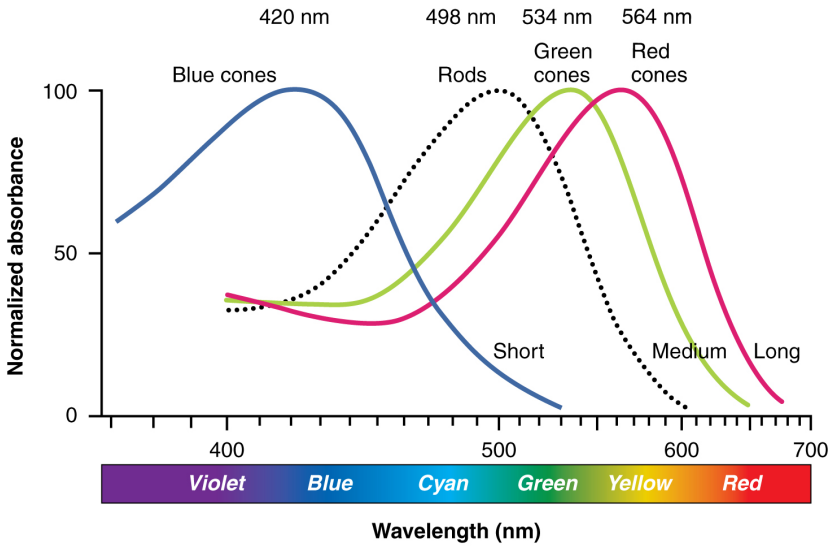


FIGURE 14.18 Comparison of Color Sensitivity of Photopigments Comparing the peak sensitivity and absorbance spectra of the four photopigments suggests that they are most sensitive to particular wavelengths.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/occipital) to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where "seeing," or visual perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that "specialized cells in the retina called ganglion cells convert the light rays into electrical signals." What aspect of retinal processing is simplified by that statement? Explain your answer.

Sensory Nerves

Once any sensory cell transduces a stimulus into a nerve impulse, that impulse has to travel along axons to reach the CNS. In many of the special senses, the axons leaving the sensory receptors have a **topographical** arrangement, meaning that the location of the sensory receptor relates to the location of the axon in the nerve. For example, in the retina, axons from RGCs in the fovea are located at the center of the optic nerve, where they are surrounded by axons from the more peripheral RGCs.

Spinal Nerves

Generally, spinal nerves contain afferent axons from sensory receptors in the periphery, such as from the skin, mixed with efferent axons travelling to the muscles or other effector organs. As the spinal nerve nears the spinal cord, it splits into dorsal and ventral roots. The dorsal root contains only the axons of sensory neurons, whereas the ventral roots contain only the axons of the motor neurons. Some of the branches will synapse with local neurons in the dorsal root ganglion, posterior (dorsal) horn, or even the anterior (ventral) horn, at the level of the spinal cord where they enter. Other branches will travel a short distance up or down the spine to interact with neurons at other levels of the spinal cord. A branch may also turn into the posterior (dorsal) column of the white matter to connect

ascend the brain stem as a bundle called the **medial lemniscus**. These axons terminate in the thalamus, where each synapses with the third neuron in their respective pathway. The third neuron in the system projects its axons to the postcentral gyrus of the cerebral cortex, where somatosensory stimuli are initially processed and the conscious perception of the stimulus occurs.

The spinothalamic tract also begins with neurons in a dorsal root ganglion. These neurons extend their axons to the dorsal horn, where they synapse with the second neuron in their respective pathway. The name "spinothalamic" comes from this second neuron, which has its cell body in the spinal cord gray matter and connects to the thalamus. Axons from these second neurons then decussate within the spinal cord and ascend to the brain and enter the thalamus, where each synapses with the third neuron in its respective pathway. The neurons in the thalamus then project their axons to the spinothalamic tract, which synapses in the postcentral gyrus of the cerebral cortex.

These two systems are similar in that they both begin with dorsal root ganglion cells, as with most general sensory information. The dorsal column system is primarily responsible for touch sensations and proprioception, whereas the spinothalamic tract pathway is primarily responsible for pain and temperature sensations. Another similarity is that the second neurons in both of these pathways are contralateral, because they project across the midline to the other side of the brain or spinal cord. In the dorsal column system, this decussation takes place in the brain stem; in the spinothalamic pathway, it takes place in the spinal cord at the same spinal cord level at which the information entered. The third neurons in the two pathways are essentially the same. In both, the second neuron synapses in the thalamus, and the thalamic neuron projects to the somatosensory cortex.

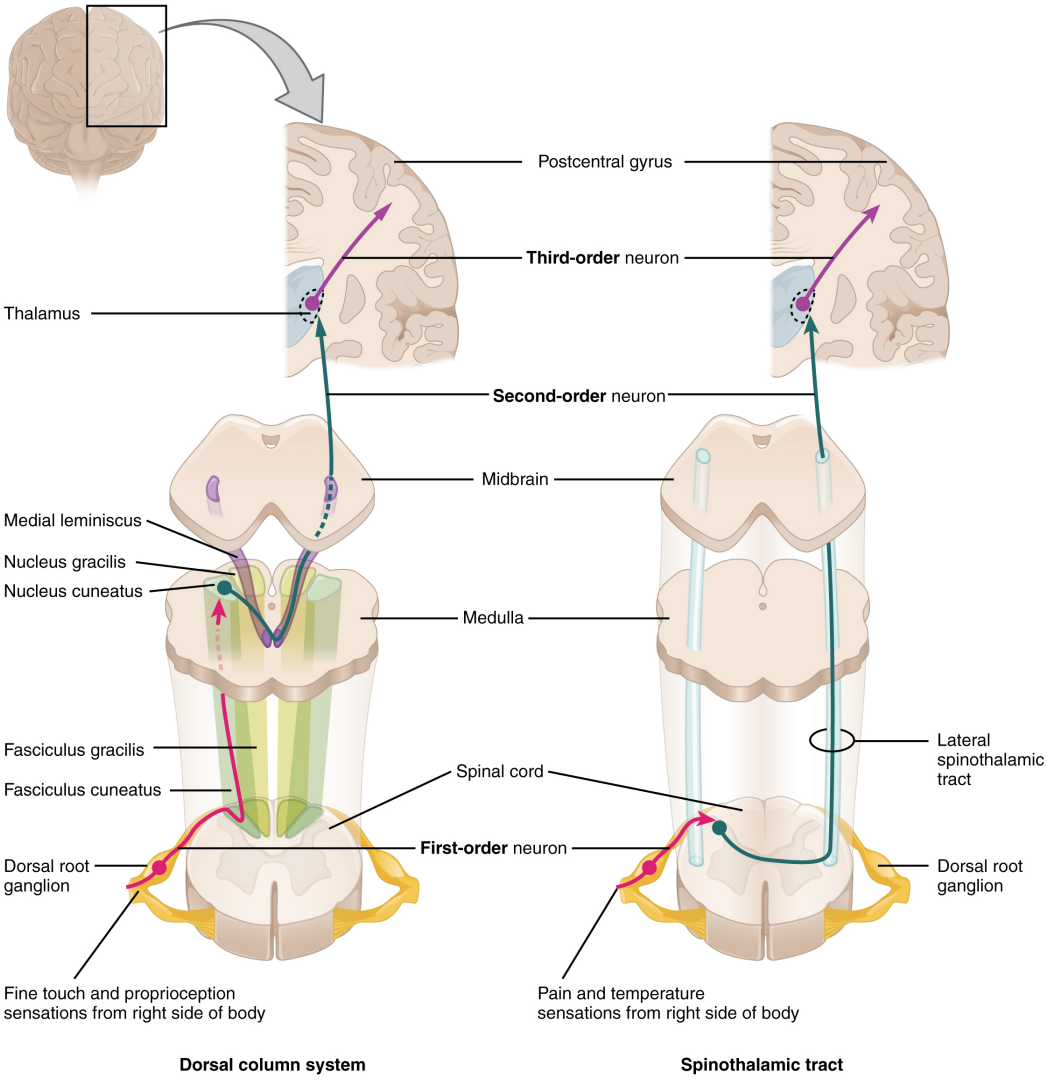


FIGURE 14.19 Anterior View of Ascending Sensory Pathways of the Spinal Cord The dorsal column system and spinothalamic tract are the major ascending pathways that connect the periphery with the brain.

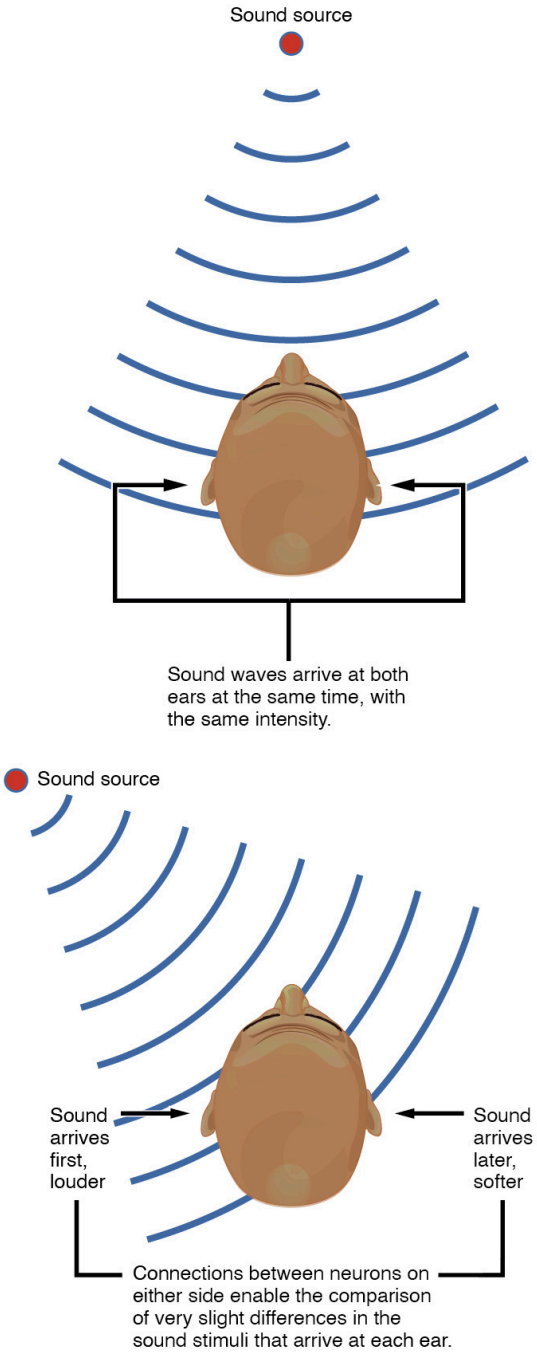


FIGURE 14.20 Auditory Brain Stem Mechanisms of Sound Localization Localizing sound in the horizontal plane is achieved by processing in the medullary nuclei of the auditory system. Connections between neurons on either side are able to compare very slight differences in sound stimuli that arrive at either ear and represent interaural time and intensity differences.

Auditory processing continues on to a nucleus in the midbrain called the **inferior colliculus**. Axons from the inferior colliculus project to two locations, the thalamus and the **superior colliculus**. The **medial geniculate nucleus** of the thalamus receives the auditory information and then projects that information to the auditory cortex in the temporal lobe of the cerebral cortex. The superior colliculus receives input from the visual and somatosensory systems, as well as the ears, to initiate stimulation of the muscles that turn the head and neck toward the auditory stimulus.

Balance is coordinated through the vestibular system, the nerves of which are composed of axons from the vestibular ganglion that carries information from the utricle, saccule, and semicircular canals. The system contributes to controlling head and neck movements in response to vestibular signals. An important function of the vestibular system is coordinating eye and head movements to maintain visual attention. Most of the axons terminate in the **vestibular nuclei** of the medulla. Some axons project from the vestibular ganglion directly to the cerebellum,

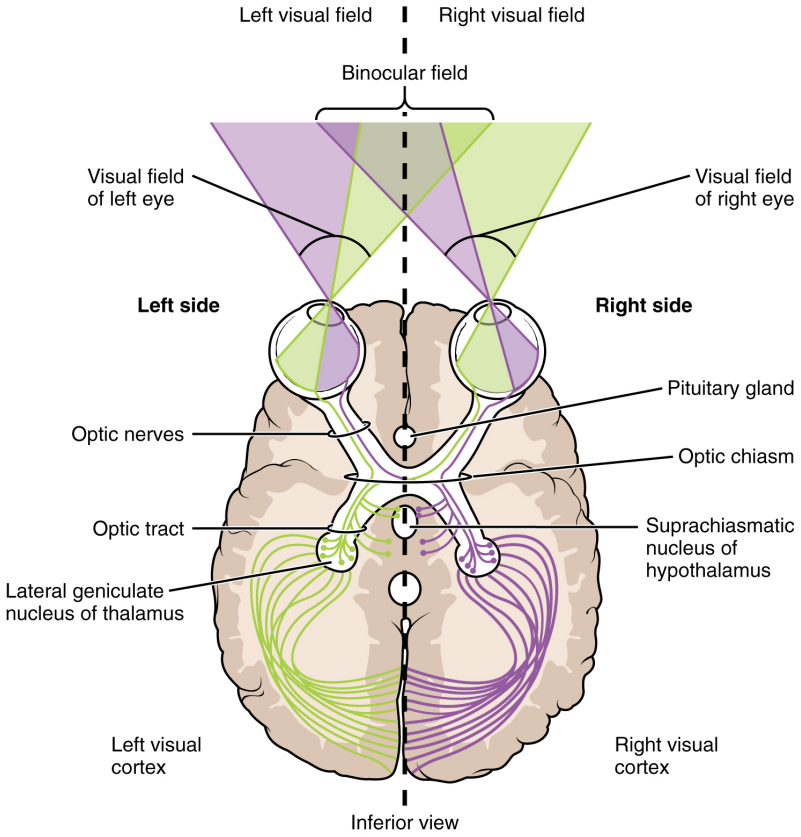


FIGURE 14.22 Segregation of Visual Field Information at the Optic Chiasm Contralateral visual field information from the lateral retina projects to the ipsilateral brain, whereas ipsilateral visual field information has to decussate at the optic chiasm to reach the opposite side of the brain. (Note that this is an inferior view.)

A unique clinical presentation that relates to this anatomic arrangement is the loss of lateral peripheral vision, known as bilateral hemianopia. This is different from "tunnel vision" because the superior and inferior peripheral fields are not lost. Visual field deficits can be disturbing for a patient, but in this case, the cause is not within the visual system itself. A growth of the pituitary gland presses against the optic chiasm and interferes with signal transmission. However, the axons projecting to the same side of the brain are unaffected. Therefore, the patient loses the outermost areas of their field of vision and cannot see objects to their right and left.

Extending from the optic chiasm, the axons of the visual system are referred to as the **optic tract** instead of the optic nerve. The optic tract has three major targets, two in the diencephalon and one in the midbrain. The connection between the eyes and diencephalon is demonstrated during development, in which the neural tissue of the retina differentiates from that of the diencephalon by the growth of the secondary vesicles. The connections of the retina into the CNS are a holdover from this developmental association. The majority of the connections of the optic tract are to the thalamus—specifically, the **lateral geniculate nucleus**. Axons from this nucleus then project to the visual cortex of the cerebrum, located in the occipital lobe. Another target of the optic tract is the superior colliculus.

In addition, a very small number of RGC axons project from the optic chiasm to the **suprachiasmatic nucleus** of the hypothalamus. These RGCs are photosensitive, in that they respond to the presence or absence of light. Unlike the photoreceptors, however, these photosensitive RGCs cannot be used to perceive images. By simply responding to the absence or presence of light, these RGCs can send information about day length. The perceived proportion of sunlight to darkness establishes the **circadian rhythm** of our bodies, allowing certain physiological events to occur at approximately the same time every day.

Diencephalon

The diencephalon is beneath the cerebrum and includes the thalamus and hypothalamus. In the somatic nervous system, the thalamus is an important relay for communication between the cerebrum and the rest of the nervous system. The hypothalamus has both somatic and autonomic functions. In addition, the hypothalamus communicates with the limbic system, which controls emotions and memory functions.

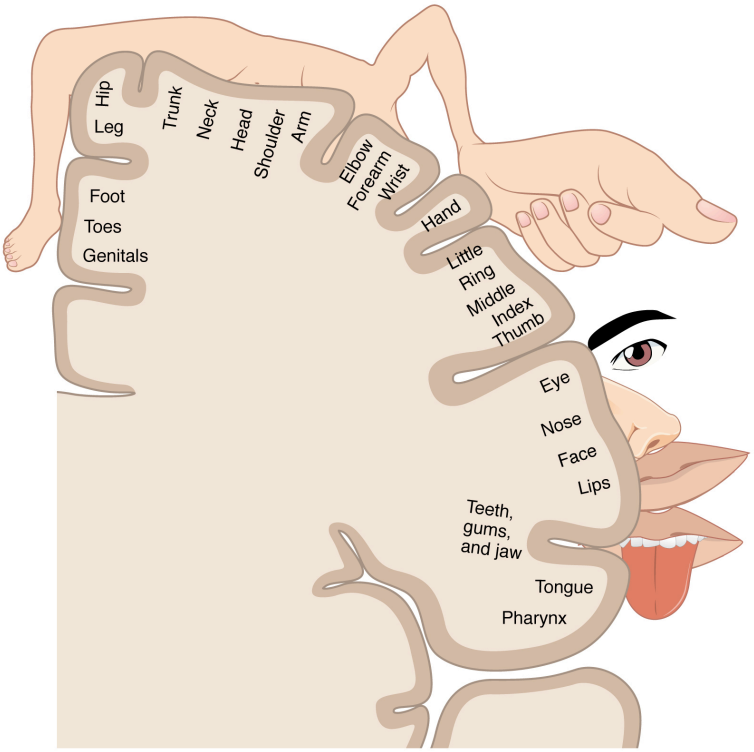


FIGURE 14.23 The Sensory Homunculus A cartoon representation of the sensory homunculus arranged adjacent to the cortical region in which the processing takes place.

Likewise, the topographic relationship between the retina and the visual cortex is maintained throughout the visual pathway. The visual field is projected onto the two retinae, as described above, with sorting at the optic chiasm. The right peripheral visual field falls on the medial portion of the right retina and the lateral portion of the left retina. The right medial retina then projects across the midline through the optic chiasm. This results in the right visual field being processed in the left visual cortex. Likewise, the left visual field is processed in the right visual cortex (see Figure 14.22). Though the chiasm is helping to sort right and left visual information, superior and inferior visual information is maintained topographically in the visual pathway. Light from the superior visual field falls on the inferior retina, and light from the inferior visual field falls on the superior retina. This topography is maintained such that the superior region of the visual cortex processes the inferior visual field and vice versa. Therefore, the visual field information is inverted and reversed as it enters the visual cortex—up is down, and left is right. However, the cortex processes the visual information such that the final conscious perception of the visual field is correct. The topographic relationship is evident in that information from the foveal region of the retina is processed in the center of the primary visual cortex. Information from the peripheral regions of the retina are correspondingly processed toward the edges of the visual cortex. Similar to the exaggerations in the sensory homunculus of the somatosensory cortex, the foveal-processing area of the visual cortex is disproportionately larger than the areas processing peripheral vision.

In an experiment performed in the 1960s, subjects wore prism glasses so that the visual field was inverted before reaching the eye. On the first day of the experiment, subjects would duck when walking up to a table, thinking it was suspended from the ceiling. However, after a few days of acclimation, the subjects behaved as if everything were represented correctly. Therefore, the visual cortex is somewhat flexible in adapting to the information it receives from our eyes (Figure 14.24).

INTERACTIVE LINK

Watch this video (http://openstax.org/l/l_3-D1) to learn more about how the brain perceives 3-D motion. Similar to how retinal disparity offers 3-D moviegoers a way to extract 3-D information from the two-dimensional visual field projected onto the retina, the brain can extract information about movement in space by comparing what the two eyes see. If movement of a visual stimulus is leftward in one eye and rightward in the opposite eye, the brain interprets this as movement toward (or away) from the face along the midline. If both eyes see an object moving in the same direction, but at different rates, what would that mean for spatial movement?

Everyday Connection

Depth Perception, 3-D Movies, and Optical Illusions

The visual field is projected onto the retinal surface, where photoreceptors transduce light energy into neural signals for the brain to interpret. The retina is a two-dimensional surface, so it does not encode three-dimensional information. However, we can perceive depth. How is that accomplished?

Two ways in which we can extract depth information from the two-dimensional retinal signal are based on monocular cues and binocular cues, respectively. Monocular depth cues are those that are the result of information within the two-dimensional visual field. One object that overlaps another object has to be in front. Relative size differences are also a cue. For example, if a basketball appears larger than the basket, then the basket must be further away. On the basis of experience, we can estimate how far away the basket is. Binocular depth cues compare information represented in the two retinae because they do not see the visual field exactly the same.

The centers of the two eyes are separated by a small distance, which is approximately 6 to 6.5 cm in most people. Because of this offset, visual stimuli do not fall on exactly the same spot on both retinae unless we are fixated directly on them and they fall on the fovea of each retina. All other objects in the visual field, either closer or farther away than the fixated object, will fall on different spots on the retina. When vision is fixed on an object in space, closer objects will fall on the lateral retina of each eye, and more distant objects will fall on the medial retina of either eye (Figure 14.25). This is easily observed by holding a finger up in front of your face as you look at a more distant object. You will see two images of your finger that represent the two disparate images that are falling on either retina.

These depth cues, both monocular and binocular, can be exploited to make the brain think there are three dimensions in two-dimensional information. This is the basis of 3-D movies. The projected image on the screen is two dimensional, but it has disparate information embedded in it. The 3-D glasses that are available at the theater filter the information so that only one eye sees one version of what is on the screen, and the other eye sees the other version. If you take the glasses off, the image on the screen will have varying amounts of blur because both eyes are seeing both layers of information, and the third dimension will not be evident. Some optical illusions can take advantage of depth cues as well, though those are more often using monocular cues to fool the brain into seeing different parts of the scene as being at different depths.

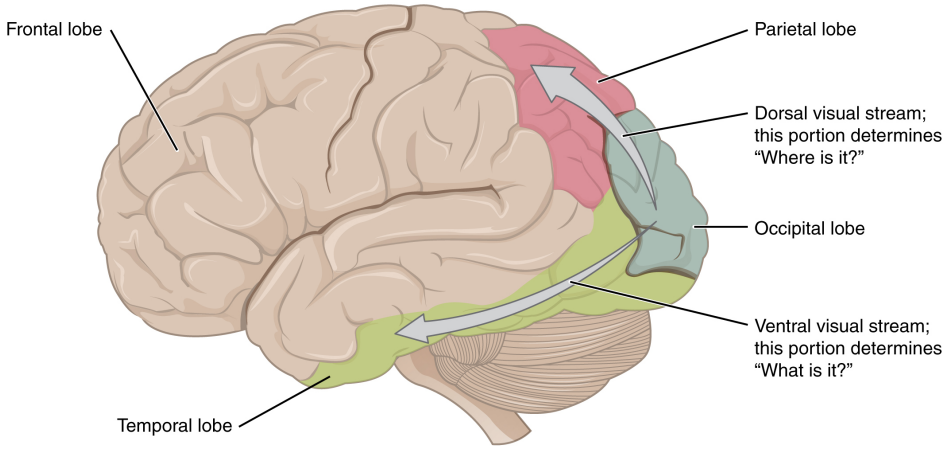


FIGURE 14.26 **Ventral and Dorsal Visual Streams** From the primary visual cortex in the occipital lobe, visual processing continues in two streams—one into the temporal lobe and one into the parietal lobe.

Disorders of the...

Brain: Prosopagnosia

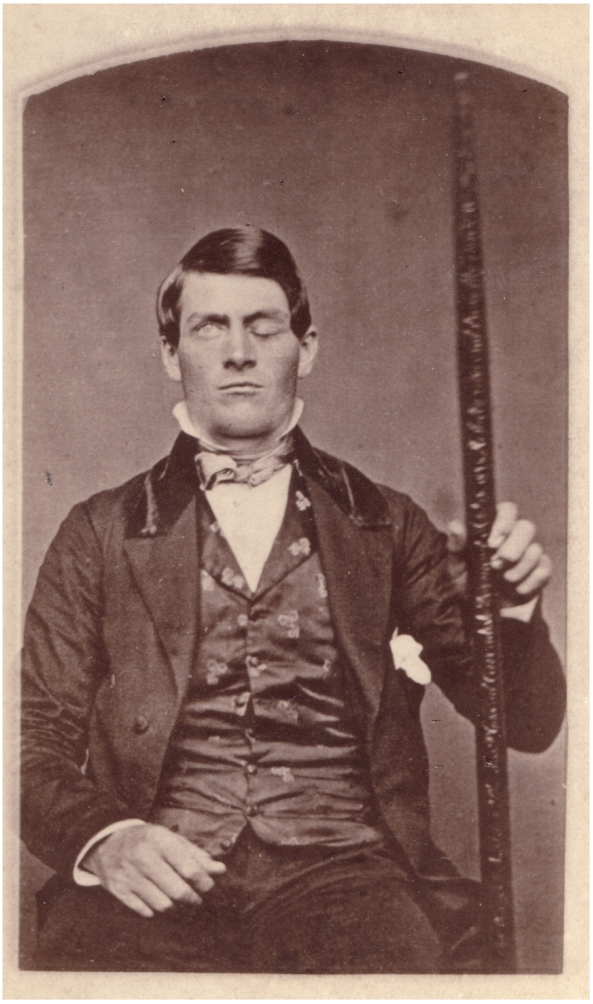
The failures of sensory perception can be unusual and debilitating. A particular sensory deficit that inhibits an important social function of humans is prosopagnosia, or face blindness. The word comes from the Greek words prosopa, that means "faces," and agnosia, that means "not knowing." Some people may feel that they cannot recognize people easily by their faces. However, a person with prosopagnosia cannot recognize the most recognizable people in their respective cultures. They would not recognize the face of a celebrity, an important historical figure, or even a family member like their mother. They may not even recognize their own face.

Prosopagnosia can be caused by trauma to the brain, or it can be present from birth. The exact cause of proposagnosia and the reason that it happens to some people is unclear. A study of the brains of people born with the deficit found that a specific region of the brain, the anterior fusiform gyrus of the temporal lobe, is often underdeveloped. This region of the brain is concerned with the recognition of visual stimuli and its possible association with memories. Though the evidence is not yet definitive, this region is likely to be where facial recognition occurs.

Though this can be a devastating condition, people who suffer from it can get by—often by using other cues to recognize the people they see. Often, the sound of a person's voice, or the presence of unique cues such as distinct facial features (a mole, for example) or hair color can help the sufferer recognize a familiar person. In the video on prosopagnosia provided in this section, a woman is shown having trouble recognizing celebrities, family members, and herself. In some situations, she can use other cues to help her recognize faces.

INTERACTIVE LINK

The inability to recognize people by their faces is a troublesome problem. It can be caused by trauma, or it may be inborn. Watch this video (http://openstax.org/l/faces) to learn more about a person who lost the ability to recognize faces as the result of an injury. She cannot recognize the faces of close family members or herself. What other information can a person suffering from prosopagnosia use to figure out whom they are seeing?



cerebrum. Penfield would probe the surface of the cortex while the patient was only under local anesthesia so that he could observe responses to the stimulation. This led to the belief that the precentral gyrus directly stimulated muscle movement. We now know that the primary motor cortex receives input from several areas that aid in planning movement, and its principle output stimulates spinal cord neurons to stimulate skeletal muscle contraction.

The primary motor cortex is arranged in a similar fashion to the primary somatosensory cortex, in that it has a topographical map of the body, creating a motor homunculus (see Figure 14.23). The neurons responsible for musculature in the feet and lower legs are in the medial wall of the precentral gyrus, with the thighs, trunk, and shoulder at the crest of the longitudinal fissure. The hand and face are in the lateral face of the gyrus. Also, the relative space allotted for the different regions is exaggerated in muscles that have greater enervation. The greatest amount of cortical space is given to muscles that perform fine, agile movements, such as the muscles of the fingers and the lower face. The "power muscles" that perform coarser movements, such as the buttock and back muscles, occupy much less space on the motor cortex.

Descending Pathways

The motor output from the cortex descends into the brain stem and to the spinal cord to control the musculature through motor neurons. Neurons located in the primary motor cortex, named **Betz cells**, are large cortical neurons that synapse with lower motor neurons in the brain stem or in the spinal cord. The two descending pathways travelled by the axons of Betz cells are the **corticobulbar tract** and the **corticospinal tract**, respectively. Both tracts are named for their origin in the cortex and their targets—either the brain stem (the term "bulbar" refers to the brain stem as the bulb, or enlargement, at the top of the spinal cord) or the spinal cord.

These two descending pathways are responsible for the conscious or voluntary movements of skeletal muscles. Any motor command from the primary motor cortex is sent down the axons of the Betz cells to activate lower motor neurons in either the cranial motor nuclei or in the ventral horn of the spinal cord. The axons of the corticobulbar tract are ipsilateral, meaning they project from the cortex to the motor nucleus on the same side of the nervous system. Conversely, the axons of the corticospinal tract are largely contralateral, meaning that they cross the midline of the brain stem or spinal cord and synapse on the opposite side of the body. Therefore, the right motor cortex of the cerebrum controls muscles on the left side of the body, and vice versa.

The corticospinal tract descends from the cortex through the deep white matter of the cerebrum. It then passes between the caudate nucleus and putamen of the basal nuclei as a bundle called the **internal capsule**. The tract then passes through the midbrain as the **cerebral peduncles**, after which it burrows through the pons. Upon entering the medulla, the tracts make up the large white matter tract referred to as the **pyramids** (Figure 14.28). The defining landmark of the medullary-spinal border is the **pyramidal decussation**, which is where most of the fibers in the corticospinal tract cross over to the opposite side of the brain. At this point, the tract separates into two parts, which have control over different domains of the musculature.

cervical enlargement is particularly large because there is greater control over the fine musculature of the upper limbs, particularly of the fingers. The **lumbar enlargement** is not as significant in appearance because there is less fine motor control of the lower limbs.

Axial Control

The **anterior corticospinal tract** is responsible for controlling the muscles of the body trunk (see Figure 14.28). These axons do not decussate in the medulla. Instead, they remain in an anterior position as they descend the brain stem and enter the spinal cord. These axons then travel to the spinal cord level at which they synapse with a lower motor neuron. Upon reaching the appropriate level, the axons decussate, entering the ventral horn on the opposite side of the spinal cord from which they entered. In the ventral horn, these axons synapse with their corresponding lower motor neurons. The lower motor neurons are located in the medial regions of the ventral horn, because they control the axial muscles of the trunk.

Because movements of the body trunk involve both sides of the body, the anterior corticospinal tract is not entirely contralateral. Some collateral branches of the tract will project into the ipsilateral ventral horn to control synergistic muscles on that side of the body, or to inhibit antagonistic muscles through interneurons within the ventral horn. Through the influence of both sides of the body, the anterior corticospinal tract can coordinate postural muscles in broad movements of the body. These coordinating axons in the anterior corticospinal tract are often considered bilateral, as they are both ipsilateral and contralateral.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/motorpathway) to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?

Extrapyramidal Controls

Other descending connections between the brain and the spinal cord are called the **extrapyramidal system**. The name comes from the fact that this system is outside the corticospinal pathway, which includes the pyramids in the medulla. A few pathways originating from the brain stem contribute to this system.

The **tectospinal tract** projects from the midbrain to the spinal cord and is important for postural movements that are driven by the superior colliculus. The name of the tract comes from an alternate name for the superior colliculus, which is the tectum. The **reticulospinal tract** connects the reticular system, a diffuse region of gray matter in the brain stem, with the spinal cord. This tract influences trunk and proximal limb muscles related to posture and locomotion. The reticulospinal tract also contributes to muscle tone and influences autonomic functions. The **vestibulospinal tract** connects the brain stem nuclei of the vestibular system with the spinal cord. This allows posture, movement, and balance to be modulated on the basis of equilibrium information provided by the vestibular system.

The pathways of the extrapyramidal system are influenced by subcortical structures. For example, connections between the secondary motor cortices and the extrapyramidal system modulate spine and cranium movements. The basal nuclei, which are important for regulating movement initiated by the CNS, influence the extrapyramidal system as well as its thalamic feedback to the motor cortex.

The conscious movement of our muscles is more complicated than simply sending a single command from the precentral gyrus down to the proper motor neurons. During the movement of any body part, our muscles relay information back to the brain, and the brain is constantly sending “revised” instructions back to the muscles. The cerebellum is important in contributing to the motor system because it compares cerebral motor commands with proprioceptive feedback. The corticospinal fibers that project to the ventral horn of the spinal cord have branches that also synapse in the pons, which project to the cerebellum. Also, the proprioceptive sensations of the dorsal column system have a collateral projection to the medulla that projects to the cerebellum. These two streams of information are compared in the cerebellar cortex. Conflicts between the motor commands sent by the cerebrum and body position information provided by the proprioceptors cause the cerebellum to stimulate the **red nucleus** of the midbrain. The red nucleus then sends corrective commands to the spinal cord along the **rubrospinal tract**. The

As you withdraw your hand from the stove, you do not want to slow that reflex down. As the biceps brachii contracts, the antagonistic triceps brachii needs to relax. Because the neuromuscular junction is strictly excitatory, the biceps will contract when the motor nerve is active. Skeletal muscles do not actively relax. Instead the motor neuron needs to "quiet down," or be inhibited. In the hot-stove withdrawal reflex, this occurs through an interneuron in the spinal cord. The interneuron's cell body is located in the dorsal horn of the spinal cord. The interneuron receives a synapse from the axon of the sensory neuron that detects that the hand is being burned. In response to this stimulation from the sensory neuron, the interneuron then inhibits the motor neuron that controls the triceps brachii. This is done by releasing a neurotransmitter or other signal that hyperpolarizes the motor neuron connected to the triceps brachii, making it less likely to initiate an action potential. With this motor neuron being inhibited, the triceps brachii relaxes. Without the antagonistic contraction, withdrawal from the hot stove is faster and keeps further tissue damage from occurring.

Another example of a withdrawal reflex occurs when you step on a painful stimulus, like a tack or a sharp rock. The nociceptors that are activated by the painful stimulus activate the motor neurons responsible for contraction of the tibialis anterior muscle. This causes dorsiflexion of the foot. An inhibitory interneuron, activated by a collateral branch of the nociceptor fiber, will inhibit the motor neurons of the gastrocnemius and soleus muscles to cancel plantar flexion. An important difference in this reflex is that plantar flexion is most likely in progress as the foot is pressing down onto the tack. Contraction of the tibialis anterior is not the most important aspect of the reflex, as continuation of plantar flexion will result in further damage from stepping onto the tack.

Another type of reflex is a **stretch reflex**. In this reflex, when a skeletal muscle is stretched, a muscle spindle receptor is activated. The axon from this receptor structure will cause direct contraction of the muscle. A collateral of the muscle spindle fiber will also inhibit the motor neuron of the antagonist muscles. The reflex helps to maintain muscles at a constant length. A common example of this reflex is the knee jerk that is elicited by a rubber hammer struck against the patellar ligament in a physical exam.

A specialized reflex to protect the surface of the eye is the **corneal reflex**, or the eye blink reflex. When the cornea is stimulated by a tactile stimulus, or even by bright light in a related reflex, blinking is initiated. The sensory component travels through the trigeminal nerve, which carries somatosensory information from the face, or through the optic nerve, if the stimulus is bright light. The motor response travels through the facial nerve and innervates the orbicularis oculi on the same side. This reflex is commonly tested during a physical exam using an air puff or a gentle touch of a cotton-tipped applicator.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/reflexarc) to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/newreflex) to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

encapsulated ending configuration of a sensory receptor neuron with dendrites surrounded by specialized structures to aid in transduction of a particular type of sensation, such as the lamellated corpuscles in the deep dermis and subcutaneous tissue

equilibrium sense of balance that includes sensations of position and movement of the head

executive functions cognitive processes of the prefrontal cortex that lead to directing goal-directed behavior, which is a precursor to executing motor commands

external ear structures on the lateral surface of the head, including the auricle and the ear canal back to the tympanic membrane

exteroceptor sensory receptor that is positioned to interpret stimuli from the external environment, such as photoreceptors in the eye or somatosensory receptors in the skin

extraocular muscle one of six muscles originating out of the bones of the orbit and inserting into the surface of the eye which are responsible for moving the eye

extrapyramidal system pathways between the brain and spinal cord that are separate from the corticospinal tract and are responsible for modulating the movements generated through that primary pathway

fasciculus cuneatus lateral division of the dorsal column system composed of fibers from sensory neurons in the upper body

fasciculus gracilis medial division of the dorsal column system composed of fibers from sensory neurons in the lower body

fibrous tunic outer layer of the eye primarily composed of connective tissue known as the sclera and cornea

fovea exact center of the retina at which visual stimuli are focused for maximal acuity, where the retina is thinnest, at which there is nothing but photoreceptors

free nerve ending configuration of a sensory receptor neuron with dendrites in the connective tissue of the organ, such as in the dermis of the skin, that are most often sensitive to chemical, thermal, and mechanical stimuli

frontal eye fields area of the prefrontal cortex responsible for moving the eyes to attend to visual stimuli

general sense any sensory system that is distributed throughout the body and incorporated into organs of multiple other systems, such as the walls of the digestive organs or the skin

gustation sense of taste

gustatory receptor cells sensory cells in the taste bud that transduce the chemical stimuli of gustation

hair cells mechanoreceptor cells found in the inner ear that transduce stimuli for the senses of hearing and balance

incus (also, anvil) ossicle of the middle ear that connects the malleus to the stapes

inferior colliculus last structure in the auditory brainstem pathway that projects to the thalamus and superior colliculus

inferior oblique extraocular muscle responsible for lateral rotation of the eye

inferior rectus extraocular muscle responsible for looking down

inner ear structure within the temporal bone that contains the sensory apparati of hearing and balance

inner segment in the eye, the section of a photoreceptor that contains the nucleus and other major organelles for normal cellular functions

inner synaptic layer layer in the retina where bipolar cells connect to RGCs

interaural intensity difference cue used to aid sound localization in the horizontal plane that compares the relative loudness of sounds at the two ears, because the ear closer to the sound source will hear a slightly more intense sound

interaural time difference cue used to help with sound localization in the horizontal plane that compares the relative time of arrival of sounds at the two ears, because the ear closer to the sound source will receive the stimulus microseconds before the other ear

internal capsule segment of the descending motor pathway that passes between the caudate nucleus and the putamen

interoceptor sensory receptor that is positioned to interpret stimuli from internal organs, such as stretch receptors in the wall of blood vessels

ipsilateral word meaning on the same side, as in axons that do not cross the midline in a fiber tract

iris colored portion of the anterior eye that surrounds the pupil

kinesthesia sense of body movement based on sensations in skeletal muscles, tendons, joints, and the skin

lacrimal duct duct in the medial corner of the orbit that drains tears into the nasal cavity

lacrimal gland gland lateral to the orbit that produces tears to wash across the surface of the eye

lateral corticospinal tract division of the

from the 11-*cis*-retinal isomer to the all-*trans*-retinal isomer

photon individual "packet" of light

photoreceptor receptor cell specialized to respond to light stimuli

premotor cortex cortical area anterior to the primary motor cortex that is responsible for planning movements

primary sensory cortex region of the cerebral cortex that initially receives sensory input from an ascending pathway from the thalamus and begins the processing that will result in conscious perception of that modality

proprioception sense of position and movement of the body

proprioceptor receptor cell that senses changes in the position and kinesthetic aspects of the body

pupil open hole at the center of the iris that light passes through into the eye

pyramidal decussation location at which corticospinal tract fibers cross the midline and segregate into the anterior and lateral divisions of the pathway

pyramids segment of the descending motor pathway that travels in the anterior position of the medulla

receptor cell cell that transduces environmental stimuli into neural signals

red nucleus midbrain nucleus that sends corrective commands to the spinal cord along the rubrospinal tract, based on disparity between an original command and the sensory feedback from movement

reticulospinal tract extrapyramidal connections between the brain stem and spinal cord that modulate movement, contribute to posture, and regulate muscle tone

retina nervous tissue of the eye at which phototransduction takes place

retinal cofactor in an opsin molecule that undergoes a biochemical change when struck by a photon (pronounced with a stress on the last syllable)

retinal ganglion cell (RGC) neuron of the retina that projects along the second cranial nerve

rhodopsin photopigment molecule found in the rod photoreceptors

rod photoreceptor one of the two types of retinal receptor cell that is specialized for low-light vision

round window membrane that marks the end of the scala tympani

rubrospinal tract descending motor control pathway, originating in the red nucleus, that mediates control of the limbs on the basis of cerebellar processing

saccule structure of the inner ear responsible for transducing linear acceleration in the vertical plane

scala tympani portion of the cochlea that extends from the apex to the round window

scala vestibuli portion of the cochlea that extends from the oval window to the apex

sclera white of the eye

semicircular canals structures within the inner ear responsible for transducing rotational movement information

sensory homunculus topographic representation of the body within the somatosensory cortex demonstrating the correspondence between neurons processing stimuli and sensitivity

sensory modality a particular system for interpreting and perceiving environmental stimuli by the nervous system

solitary nucleus medullar nucleus that receives taste information from the facial and glossopharyngeal nerves

somatosensation general sense associated with modalities lumped together as touch

special sense any sensory system associated with a specific organ structure, namely smell, taste, sight, hearing, and balance

spinal trigeminal nucleus component of the trigeminal nuclei that is found in the medulla

spinothalamic tract ascending tract of the spinal cord associated with pain and temperature sensations

spiral ganglion location of neuronal cell bodies that transmit auditory information along the eighth cranial nerve

stapes (also, stirrup) ossicle of the middle ear that is attached to the inner ear

stereocilia array of apical membrane extensions in a hair cell that transduce movements when they are bent

stretch reflex response to activation of the muscle spindle stretch receptor that causes contraction of the muscle to maintain a constant length

submodality specific sense within a broader major sense such as sweet as a part of the sense of taste, or color as a part of vision

superior colliculus structure in the midbrain that combines visual, auditory, and somatosensory input to coordinate spatial and topographic representations of the three sensory systems

superior oblique extraocular muscle responsible for medial rotation of the eye

superior rectus extraocular muscle responsible for looking up

supplemental motor area cortical area anterior to the primary motor cortex that is responsible for

for fluid balance and pain reception, respectively. Mechanoreceptors respond to mechanical stimuli and are the basis for most aspects of somatosensation, as well as being the basis of audition and equilibrium in the inner ear. Thermoreceptors are sensitive to temperature changes, and photoreceptors are sensitive to light energy.

The nerves that convey sensory information from the periphery to the CNS are either spinal nerves, connected to the spinal cord, or cranial nerves, connected to the brain. Spinal nerves have mixed populations of fibers; some are motor fibers and some are sensory. The sensory fibers connect to the spinal cord through the dorsal root, which is attached to the dorsal root ganglion. Sensory information from the body that is conveyed through spinal nerves will project to the opposite side of the brain to be processed by the cerebral cortex. The cranial nerves can be strictly sensory fibers, such as the olfactory, optic, and vestibulocochlear nerves, or mixed sensory and motor nerves, such as the trigeminal, facial, glossopharyngeal, and vagus nerves. The cranial nerves are connected to the same side of the brain from which the sensory information originates.

14.2 Central Processing

Sensory input to the brain enters through pathways that travel through either the spinal cord (for somatosensory input from the body) or the brain stem (for everything else, except the visual and olfactory systems) to reach the diencephalon. In the diencephalon, sensory pathways reach the thalamus. This is necessary for all sensory systems to reach the cerebral cortex, except for the olfactory system that is directly connected to the frontal and temporal lobes.

The two major tracts in the spinal cord, originating from sensory neurons in the dorsal root ganglia, are the dorsal column system and the spinothalamic tract. The major differences between the two are in the type of information that is relayed to the brain and where the tracts decussate. The dorsal column system primarily carries information about touch and proprioception and crosses the midline in the medulla. The spinothalamic tract is primarily responsible for pain and temperature sensation and crosses the midline in the spinal cord at the level at which it enters. The trigeminal nerve adds similar sensation information from the head to these pathways.

The auditory pathway passes through multiple nuclei in the brain stem in which additional information is extracted from the basic frequency stimuli processed by the cochlea. Sound localization is made possible through the activity of these brain stem structures. The vestibular system enters the brain stem and influences activity in the cerebellum, spinal cord, and cerebral cortex.

The visual pathway segregates information from the two eyes so that one half of the visual field projects to the other side of the brain. Within visual cortical areas, the perception of the stimuli and their location is passed along two streams, one ventral and one dorsal. The ventral visual stream connects to structures in the temporal lobe that are important for long-term memory formation. The dorsal visual stream interacts with the somatosensory cortex in the parietal lobe, and together they can influence the activity in the frontal lobe to generate movements of the body in relation to visual information.

14.3 Motor Responses

The motor components of the somatic nervous system begin with the frontal lobe of the brain, where the prefrontal cortex is responsible for higher functions such as working memory. The integrative and associate functions of the prefrontal lobe feed into the secondary motor areas, which help plan movements. The premotor cortex and supplemental motor area then feed into the primary motor cortex that initiates movements. Large Betz cells project through the corticobulbar and corticospinal tracts to synapse on lower motor neurons in the brain stem and ventral horn of the spinal cord, respectively. These connections are responsible for generating movements of skeletal muscles.

The extrapyramidal system includes projections from the brain stem and higher centers that influence movement, mostly to maintain balance and posture, as well as to maintain muscle tone. The superior colliculus and red nucleus in the midbrain, the vestibular nuclei in the medulla, and the reticular formation throughout the brain stem each have tracts projecting to the spinal cord in this system. Descending input from the secondary motor cortices, basal nuclei, and cerebellum connect to the origins of these tracts in the brain stem.

All of these motor pathways project to the spinal cord to synapse with motor neurons in the ventral horn of the spinal cord. These lower motor neurons are the cells that connect to skeletal muscle and cause contractions. These neurons project through the spinal nerves to connect to the muscles at neuromuscular junctions. One motor neuron connects to multiple muscle fibers within a target muscle. The number of fibers that are innervated by a single motor neuron varies on the basis of the precision necessary for that

6. Watch this video (http://openstax.org/l/l_3-D1) to learn more about how the brain perceives 3-D motion. Similar to how retinal disparity offers 3-D moviegoers a way to extract 3-D information from the two-dimensional visual field projected onto the retina, the brain can extract information about movement in space by comparing what the two eyes see. If movement of a visual stimulus is leftward in one eye and rightward in the opposite eye, the brain interprets this as movement toward (or away) from the face along the midline. If both eyes see an object moving in the same direction, but at different rates, what would that mean for spatial movement?
7. The inability to recognize people by their faces is a troublesome problem. It can be caused by trauma, or it may be inborn. Watch this video (http://openstax.org/l/faces) to learn more about a person who lost the ability to recognize faces as the result of an injury. She cannot recognize the faces of close family members or herself. What other information can a person suffering from prosopagnosia use to figure out whom they are seeing?
8. Watch this video (http://openstax.org/l/motorpathway) to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?
9. Visit this site (http://openstax.org/l/NYTmotor) to read about an elderly woman who starts to lose the ability to control fine movements, such as speech and the movement of limbs. Many of the usual causes were ruled out. It was not a stroke, Parkinson's disease, diabetes, or thyroid dysfunction. The next most obvious cause was medication, so her pharmacist had to be consulted. The side effect of a drug meant to help her sleep had resulted in changes in motor control. What regions of the nervous system are likely to be the focus of haloperidol side effects?
10. Watch this video (http://openstax.org/l/reflexarc) to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.
11. Watch this video (http://openstax.org/l/newreflex) to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

Review Questions

12. What type of receptor cell is responsible for transducing pain stimuli?
    a. mechanoreceptor
    b. nociceptor
    c. osmoreceptor
    d. photoreceptor

13. Which of these cranial nerves is part of the gustatory system?
    a. olfactory
    b. trochlear
    c. trigeminal
    d. facial

14. Which submodality of taste is sensitive to the pH of saliva?
    a. umami
    b. sour
    c. bitter
    d. sweet

15. Axons from which neuron in the retina make up the optic nerve?
    a. amacrine cells
    b. photoreceptors
    c. bipolar cells
    d. retinal ganglion cells

31. The prefrontal lobotomy is a drastic—and largely out-of-practice—procedure used to disconnect that portion of the cerebral cortex from the rest of the frontal lobe and the diencephalon as a psychiatric therapy. Why would this have been thought necessary for someone with a potentially uncontrollable behavior?

32. If a reflex is a limited circuit within the somatic system, why do physical and neurological exams include them to test the health of an individual?

and the fight-or-flight response probably sounds like a panic attack. In the modern world, these sorts of reactions are associated with anxiety as much as with response to a threat. It is engrained in the nervous system to respond like this. In fact, the adaptations of the autonomic nervous system probably predate the human species and are likely to be common to all mammals, and perhaps shared by many animals. That lioness might herself be threatened in some other situation.

However, the autonomic nervous system is not just about responding to threats. Besides the fight-or-flight response, there are the responses referred to as "rest and digest." If that lioness is successful in her hunting, then she is going to rest from the exertion. Her heart rate will slow. Breathing will return to normal. The digestive system has a big job to do. Much of the function of the autonomic system is based on the connections within an autonomic, or visceral, reflex.

15.1 Divisions of the Autonomic Nervous System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Name the components that generate the sympathetic and parasympathetic responses of the autonomic nervous system
- Explain the differences in output connections within the two divisions of the autonomic nervous system
- Describe the signaling molecules and receptor proteins involved in communication within the two divisions of the autonomic nervous system

The nervous system can be divided into two functional parts: the somatic nervous system and the autonomic nervous system. The major differences between the two systems are evident in the responses that each produces. The somatic nervous system causes contraction of skeletal muscles. The autonomic nervous system controls cardiac and smooth muscle, as well as glandular tissue. The somatic nervous system is associated with voluntary responses (though many can happen without conscious awareness, like breathing), and the autonomic nervous system is associated with involuntary responses, such as those related to homeostasis.

The autonomic nervous system regulates many of the internal organs through a balance of two aspects, or divisions. In addition to the endocrine system, the autonomic nervous system is instrumental in homeostatic mechanisms in the body. The two divisions of the autonomic nervous system are the **sympathetic division** and the **parasympathetic division**. The sympathetic system is associated with the **fight-or-flight response**, and parasympathetic activity is referred to by the epithet of **rest and digest**. Homeostasis is the balance between the two systems. At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/fightflight) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?

Sympathetic Division of the Autonomic Nervous System

To respond to a threat—to fight or to run away—the sympathetic system causes divergent effects as many different effector organs are activated together for a common purpose. More oxygen needs to be inhaled and delivered to skeletal muscle. The respiratory, cardiovascular, and musculoskeletal systems are all activated together. Additionally, sweating keeps the excess heat that comes from muscle contraction from causing the body to overheat. The digestive system shuts down so that blood is not absorbing nutrients when it should be delivering oxygen to skeletal muscles. To coordinate all these responses, the connections in the sympathetic system diverge

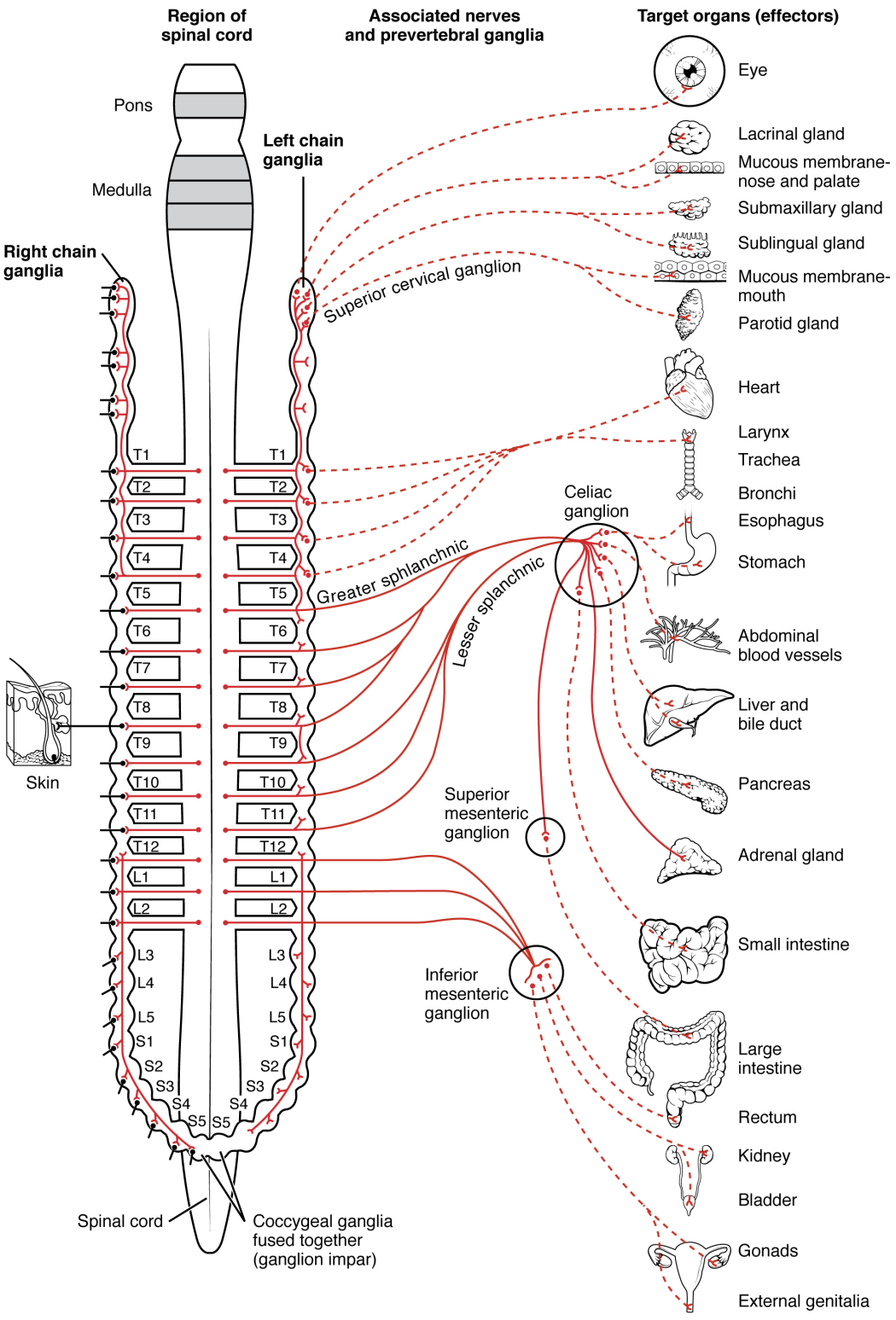


FIGURE 15.2 Connections of Sympathetic Division of the Autonomic Nervous System Neurons from the lateral horn of the spinal cord (preganglionic nerve fibers - solid lines)) project to the chain ganglia on either side of the vertebral column or to collateral (prevertebral) ganglia that are anterior to the vertebral column in the abdominal cavity. Axons from these ganglionic neurons (postganglionic nerve fibers - dotted lines) then project to target effectors throughout the body.

To continue with the analogy of the circuit diagram, there are three different types of "junctions" that operate within the sympathetic system (Figure 15.3). The first type is most direct: the sympathetic nerve projects to the chain ganglion at the same level as the **target effector** (the organ, tissue, or gland to be innervated). An example of this type is spinal nerve T1 that synapses with the T1 chain ganglion to innervate the trachea. The fibers of this branch

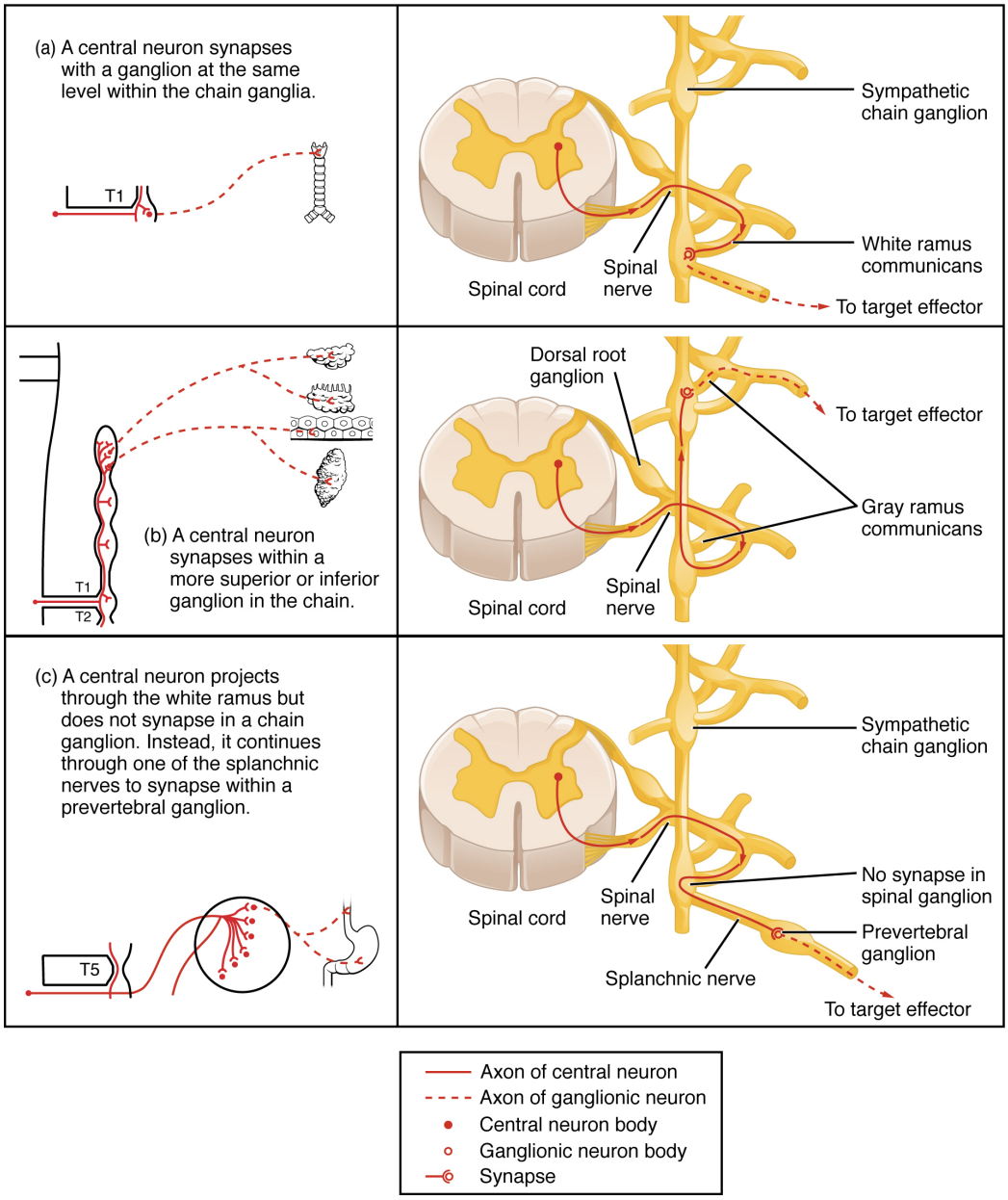


FIGURE 15.3 Sympathetic Connections and Chain Ganglia The axon from a central sympathetic neuron in the spinal cord can project to the periphery in a number of different ways. (a) The fiber can project out to the ganglion at the same level and synapse on a ganglionic neuron. (b) A branch can project to more superior or inferior ganglion in the chain. (c) A branch can project through the white ramus communicans, but not terminate on a ganglionic neuron in the chain. Instead, it projects through one of the splanchnic nerves to a collateral ganglion or the adrenal medulla (not pictured).

An axon from the central neuron that projects to a sympathetic ganglion is referred to as a **preganglionic fiber** or neuron, and represents the output from the CNS to the ganglion. Because the sympathetic ganglia are adjacent to the vertebral column, preganglionic sympathetic fibers are relatively short, and they are myelinated. A **postganglionic fiber**—the axon from a ganglionic neuron that projects to the target effector—represents the output of a ganglion that directly influences the organ. Compared with the preganglionic fibers, postganglionic sympathetic fibers are long because of the relatively greater distance from the ganglion to the target effector. These fibers are unmyelinated. (Note that the term "postganglionic neuron" may be used to describe the projection from a ganglion to the target. The problem with that usage is that the cell body is in the ganglion, and only the fiber is postganglionic. Typically, the term neuron applies to the entire cell.)

One type of preganglionic sympathetic fiber does not terminate in a ganglion. These are the axons from central sympathetic neurons that project to the **adrenal medulla**, the interior portion of the adrenal gland. These axons are

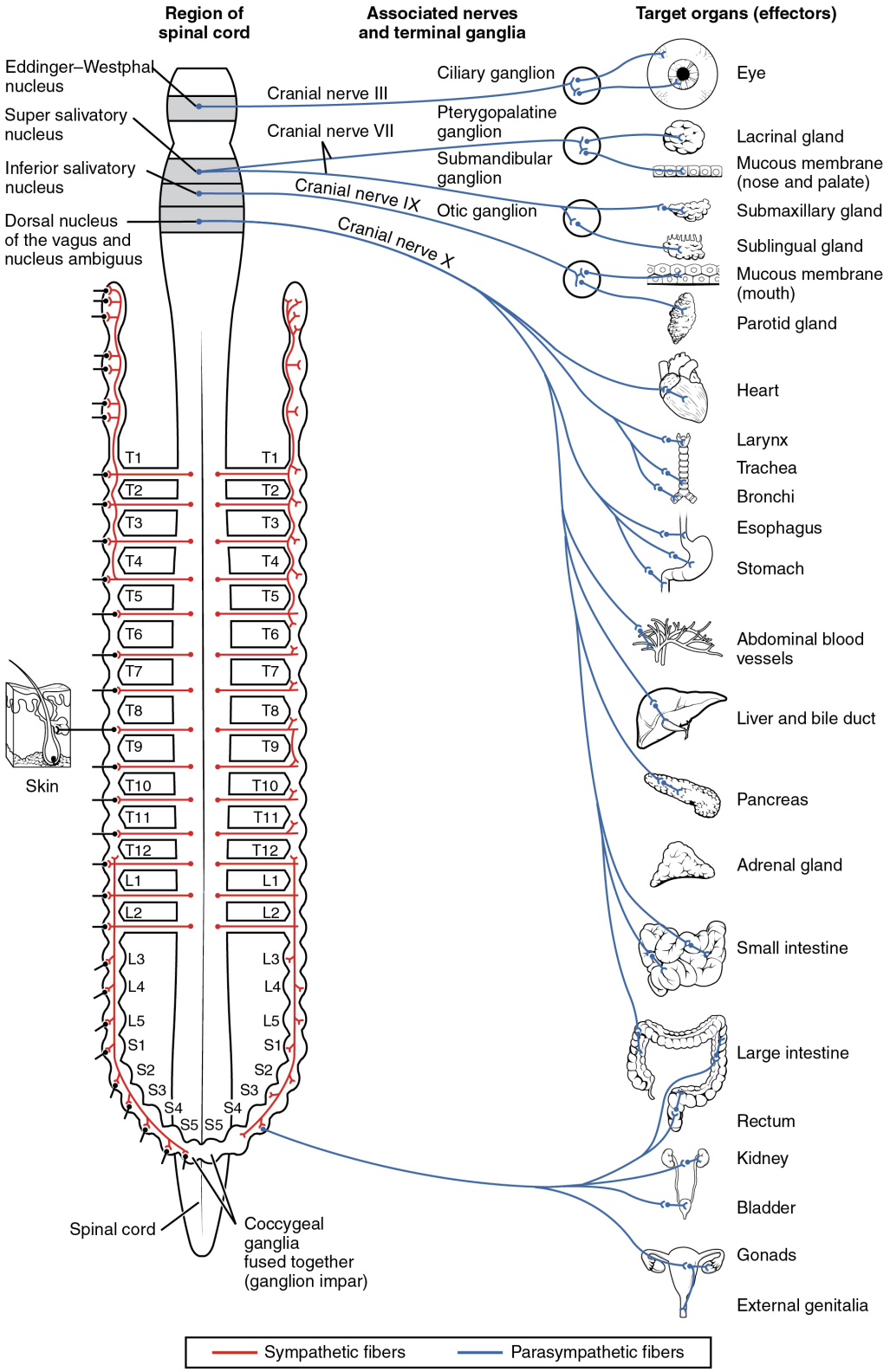


FIGURE 15.4 Connections of Parasympathetic Division of the Autonomic Nervous System Neurons from brain-stem nuclei, or from the lateral horn of the sacral spinal cord, project to terminal ganglia near or within the various organs of the body. Axons from these ganglionic neurons then project the short distance to those target effectors.

Chemical Signaling in the Autonomic Nervous System

Where an autonomic neuron connects with a target, there is a synapse. The electrical signal of the action potential

Autonomic System Signaling Molecules

	Sympathetic	Parasympathetic
Preganglionic	Acetylcholine → nicotinic receptor	Acetylcholine → nicotinic receptor
Postganglionic	Norepinephrine → α- or β-adrenergic receptors Acetylcholine → muscarinic receptor (associated with sweat glands and the blood vessels associated with skeletal muscles only	Acetylcholine → muscarinic receptor

TABLE 15.1

Signaling molecules can belong to two broad groups. Neurotransmitters are released at synapses, whereas hormones are released into the bloodstream. These are simplistic definitions, but they can help to clarify this point. Acetylcholine can be considered a neurotransmitter because it is released by axons at synapses. The adrenergic system, however, presents a challenge. Postganglionic sympathetic fibers release norepinephrine, which can be considered a neurotransmitter. But the adrenal medulla releases epinephrine and norepinephrine into circulation, so they should be considered hormones.

What are referred to here as synapses may not fit the strictest definition of synapse. Some sources will refer to the connection between a postganglionic fiber and a target effector as neuroeffector junctions; neurotransmitters, as defined above, would be called neuromodulators. The structure of postganglionic connections are not the typical synaptic end bulb that is found at the neuromuscular junction, but rather are chains of swellings along the length of a postganglionic fiber called a **varicosity** (Figure 15.5).

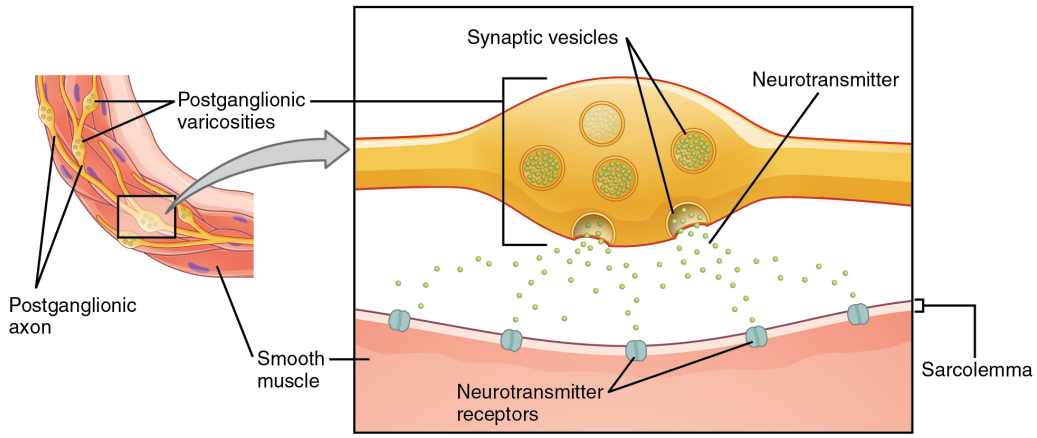


FIGURE 15.5 **Autonomic Varicosities** The connection between autonomic fibers and target effectors is not the same as the typical synapse, such as the neuromuscular junction. Instead of a synaptic end bulb, a neurotransmitter is released from swellings along the length of a fiber that makes an extended network of connections in the target effector.

Everyday Connection

Fight or Flight? What About Fright and Freeze?

The original usage of the epithet "fight or flight" comes from a scientist named Walter Cannon who worked at Harvard in 1915. The concept of homeostasis and the functioning of the sympathetic system had been introduced in France in the previous century. Cannon expanded the idea, and introduced the idea that an animal responds to a threat by preparing to stand and fight or run away. The nature of this response was thoroughly explained in a book on the physiology of pain, hunger, fear, and rage.

When students learn about the sympathetic system and the fight-or-flight response, they often stop and wonder about other responses. If you were faced with a lioness running toward you as pictured at the beginning of this

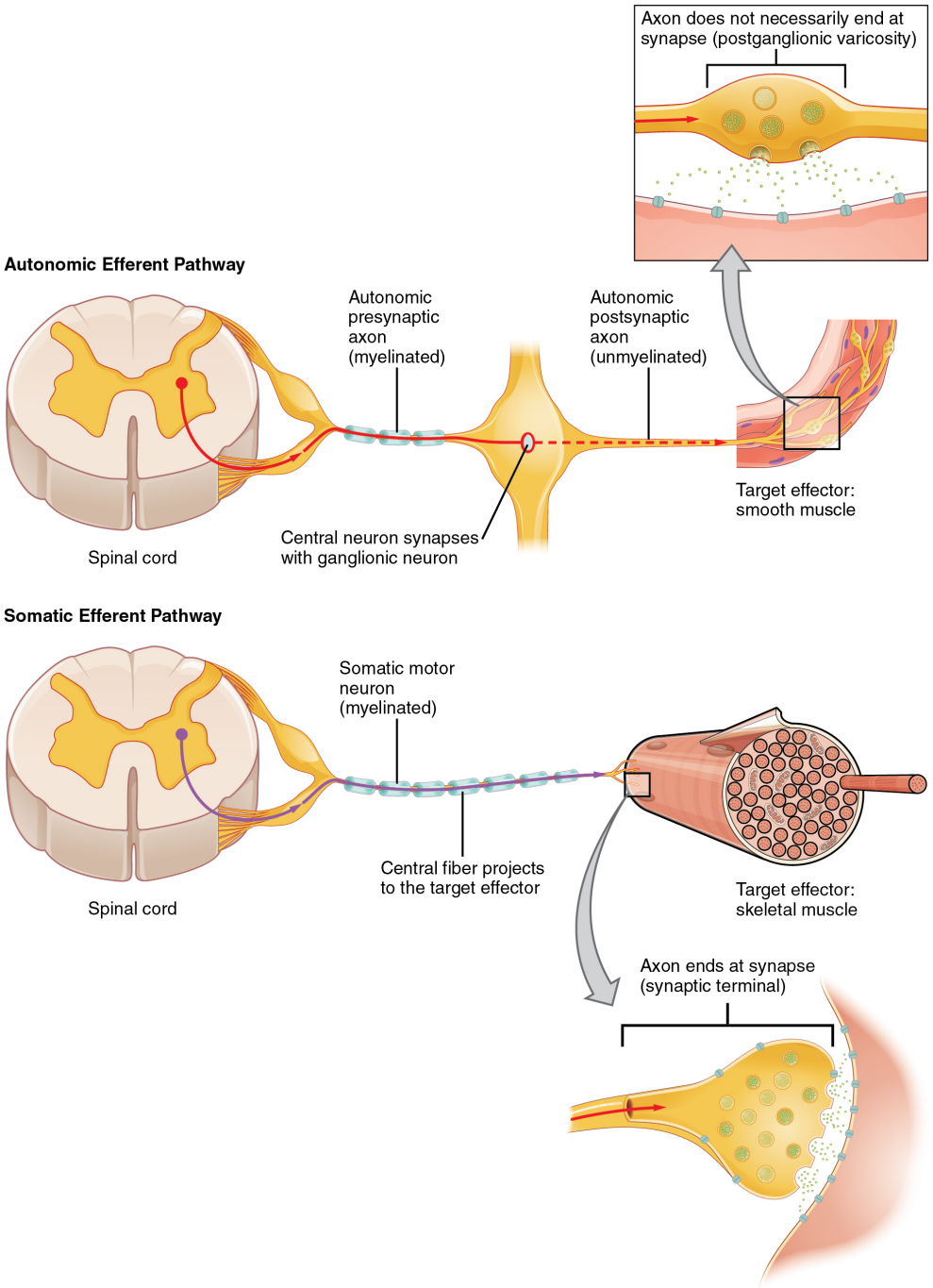


FIGURE 15.6 Comparison of Somatic and Visceral Reflexes The afferent inputs to somatic and visceral reflexes are essentially the same, whereas the efferent branches are different. Somatic reflexes, for instance, involve a direct connection from the ventral horn of the spinal cord to the skeletal muscle. Visceral reflexes involve a projection from the central neuron to a ganglion, followed by a second projection from the ganglion to the target effector.

Afferent Branch

The afferent branch of a reflex arc does differ between somatic and visceral reflexes in some instances. Many of the inputs to visceral reflexes are from special or somatic senses, but particular senses are associated with the viscera that are not part of the conscious perception of the environment through the somatic nervous system. For example, there is a specific type of mechanoreceptor, called a **baroreceptor**, in the walls of the aorta and carotid sinuses that senses the stretch of those organs when blood volume or pressure increases. You do not have a conscious perception of having high blood pressure, but that is an important afferent branch of the cardiovascular and, particularly, vasomotor reflexes. The sensory neuron is essentially the same as any other general sensory neuron. The baroreceptor apparatus is part of the ending of a unipolar neuron that has a cell body in a sensory ganglion. The

from the mid-thoracic to lower thoracic region whereas parasympathetic fibers are found in the vagus nerve, which connects in the medulla of the brain stem. However, the neck and shoulder would connect to the spinal cord at the mid-cervical level of the spinal cord. These connections do not fit with the expected correspondence of visceral and somatosensory fibers entering at the same level of the spinal cord.

The incorrect assumption would be that the visceral sensations are coming from the spleen directly. In fact, the visceral fibers are coming from the diaphragm. The nerve connecting to the diaphragm takes a special route. The phrenic nerve is connected to the spinal cord at cervical levels 3 to 5. The motor fibers that make up this nerve are responsible for the muscle contractions that drive ventilation. These fibers have left the spinal cord to enter the phrenic nerve, meaning that spinal cord damage below the mid-cervical level is not fatal by making ventilation impossible. Therefore, the visceral fibers from the diaphragm enter the spinal cord at the same level as the somatosensory fibers from the neck and shoulder.

The diaphragm plays a role in Kehr's sign because the spleen is just inferior to the diaphragm in the upper-left quadrant of the abdominopelvic cavity. When the spleen ruptures, blood spills into this region. The accumulating hemorrhage then puts pressure on the diaphragm. The visceral sensation is actually in the diaphragm, so the referred pain is in a region of the body that corresponds to the diaphragm, not the spleen.

Efferent Branch

The efferent branch of the visceral reflex arc begins with the projection from the central neuron along the preganglionic fiber. This fiber then makes a synapse on the ganglionic neuron that projects to the target effector.

The effector organs that are the targets of the autonomic system range from the iris and ciliary body of the eye to the urinary bladder and reproductive organs. The thoracolumbar output, through the various sympathetic ganglia, reaches all of these organs. The cranial component of the parasympathetic system projects from the eye to part of the intestines. The sacral component picks up with the majority of the large intestine and the pelvic organs of the urinary and reproductive systems.

Short and Long Reflexes

Somatic reflexes involve sensory neurons that connect sensory receptors to the CNS and motor neurons that project back out to the skeletal muscles. Visceral reflexes that involve the thoracolumbar or craniosacral systems share similar connections. However, there are reflexes that do not need to involve any CNS components. A **long reflex** has afferent branches that enter the spinal cord or brain and involve the efferent branches, as previously explained. A **short reflex** is completely peripheral and only involves the local integration of sensory input with motor output (Figure 15.8).

question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

Balance in Competing Autonomic Reflex Arcs

The autonomic nervous system is important for homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation). At the level of the target effector, the signal of which system is sending the message is strictly chemical. A signaling molecule binds to a receptor that causes changes in the target cell, which in turn causes the tissue or organ to respond to the changing conditions of the body.

Competing Neurotransmitters

The postganglionic fibers of the sympathetic and parasympathetic divisions both release neurotransmitters that bind to receptors on their targets. Postganglionic sympathetic fibers release norepinephrine, with a minor exception, whereas postganglionic parasympathetic fibers release ACh. For any given target, the difference in which division of the autonomic nervous system is exerting control is just in what chemical binds to its receptors. The target cells will have adrenergic and muscarinic receptors. If norepinephrine is released, it will bind to the adrenergic receptors present on the target cell, and if ACh is released, it will bind to the muscarinic receptors on the target cell.

In the sympathetic system, there are exceptions to this pattern of dual innervation. The postganglionic sympathetic fibers that contact the blood vessels within skeletal muscle and that contact sweat glands do not release norepinephrine, they release ACh. This does not create any problem because there is no parasympathetic input to the sweat glands. Sweat glands have muscarinic receptors and produce and secrete sweat in response to the presence of ACh.

At most of the other targets of the autonomic system, the effector response is based on which neurotransmitter is released and what receptor is present. For example, regions of the heart that establish heart rate are contacted by postganglionic fibers from both systems. If norepinephrine is released onto those cells, it binds to an adrenergic receptor that causes the cells to depolarize faster, and the heart rate increases. If ACh is released onto those cells, it binds to a muscarinic receptor that causes the cells to hyperpolarize so that they cannot reach threshold as easily, and the heart rate slows. Without this parasympathetic input, the heart would work at a rate of approximately 100 beats per minute (bpm). The sympathetic system speeds that up, as it would during exercise, to 120–140 bpm, for example. The parasympathetic system slows it down to the resting heart rate of 60–80 bpm.

Another example is in the control of pupillary size (Figure 15.9). The afferent branch responds to light hitting the retina. Photoreceptors are activated, and the signal is transferred to the retinal ganglion cells that send an action potential along the optic nerve into the diencephalon. If light levels are low, the sympathetic system sends a signal out through the upper thoracic spinal cord to the superior cervical ganglion of the sympathetic chain. The postganglionic fiber then projects to the iris, where it releases norepinephrine onto the radial fibers of the iris (a smooth muscle). When those fibers contract, the pupil dilates—increasing the amount of light hitting the retina. If light levels are too high, the parasympathetic system sends a signal out from the Edinger–Westphal nucleus through the oculomotor nerve. This fiber synapses in the ciliary ganglion in the posterior orbit. The postganglionic fiber then projects to the iris, where it releases ACh onto the circular fibers of the iris—another smooth muscle. When those fibers contract, the pupil constricts to limit the amount of light hitting the retina.

efferent branches of the competing reflex (dilation)?

Autonomic Tone

Organ systems are balanced between the input from the sympathetic and parasympathetic divisions. When something upsets that balance, the homeostatic mechanisms strive to return it to its regular state. For each organ system, there may be more of a sympathetic or parasympathetic tendency to the resting state, which is known as the **autonomic tone** of the system. For example, the heart rate was described above. Because the resting heart rate is the result of the parasympathetic system slowing the heart down from its intrinsic rate of 100 bpm, the heart can be said to be in parasympathetic tone.

In a similar fashion, another aspect of the cardiovascular system is primarily under sympathetic control. Blood pressure is partially determined by the contraction of smooth muscle in the walls of blood vessels. These tissues have adrenergic receptors that respond to the release of norepinephrine from postganglionic sympathetic fibers by constricting and increasing blood pressure. The hormones released from the adrenal medulla—epinephrine and norepinephrine—will also bind to these receptors. Those hormones travel through the bloodstream where they can easily interact with the receptors in the vessel walls. The parasympathetic system has no significant input to the systemic blood vessels, so the sympathetic system determines their tone.

There are a limited number of blood vessels that respond to sympathetic input in a different fashion. Blood vessels in skeletal muscle, particularly those in the lower limbs, are more likely to dilate. It does not have an overall effect on blood pressure to alter the tone of the vessels, but rather allows for blood flow to increase for those skeletal muscles that will be active in the fight-or-flight response. The blood vessels that have a parasympathetic projection are limited to those in the erectile tissue of the reproductive organs. Acetylcholine released by these postganglionic parasympathetic fibers cause the vessels to dilate, leading to the engorgement of the erectile tissue.

HOMEOSTATIC IMBALANCES

Orthostatic Hypotension

Have you ever stood up quickly and felt dizzy for a moment? This is because, for one reason or another, blood is not getting to your brain so it is briefly deprived of oxygen. When you change position from sitting or lying down to standing, your cardiovascular system has to adjust for a new challenge, keeping blood pumping up into the head while gravity is pulling more and more blood down into the legs.

The reason for this is a sympathetic reflex that maintains the output of the heart in response to postural change. When a person stands up, proprioceptors indicate that the body is changing position. A signal goes to the CNS, which then sends a signal to the upper thoracic spinal cord neurons of the sympathetic division. The sympathetic system then causes the heart to beat faster and the blood vessels to constrict. Both changes will make it possible for the cardiovascular system to maintain the rate of blood delivery to the brain. Blood is being pumped superiorly through the internal branch of the carotid arteries into the brain, against the force of gravity. Gravity is not increasing while standing, but blood is more likely to flow down into the legs as they are extended for standing. This sympathetic reflex keeps the brain well oxygenated so that cognitive and other neural processes are not interrupted.

Sometimes this does not work properly. If the sympathetic system cannot increase cardiac output, then blood pressure into the brain will decrease, and a brief neurological loss can be felt. This can be brief, as a slight "wooziness" when standing up too quickly, or a loss of balance and neurological impairment for a period of time. The name for this is orthostatic hypotension, which means that blood pressure goes below the homeostatic set point when standing. It can be the result of standing up faster than the reflex can occur, which may be referred to as a benign "head rush," or it may be the result of an underlying cause.

There are two basic reasons that orthostatic hypotension can occur. First, blood volume is too low and the sympathetic reflex is not effective. This hypovolemia may be the result of dehydration or medications that affect fluid balance, such as diuretics or vasodilators. Both of these medications are meant to lower blood pressure, which may be necessary in the case of systemic hypertension, and regulation of the medications may alleviate the problem. Sometimes increasing fluid intake or water retention through salt intake can improve the situation.

The Hypothalamus

The hypothalamus is the control center for many homeostatic mechanisms. It regulates both autonomic function and endocrine function. The roles it plays in the pupillary reflexes demonstrates the importance of this control center. The optic nerve projects primarily to the thalamus, which is the necessary relay to the occipital cortex for conscious visual perception. Another projection of the optic nerve, however, goes to the hypothalamus.

The hypothalamus then uses this visual system input to drive the pupillary reflexes. If the retina is activated by high levels of light, the hypothalamus stimulates the parasympathetic response. If the optic nerve message shows that low levels of light are falling on the retina, the hypothalamus activates the sympathetic response. Output from the hypothalamus follows two main tracts, the **dorsal longitudinal fasciculus** and the **medial forebrain bundle** (Figure 15.11). Along these two tracts, the hypothalamus can influence the Edinger–Westphal nucleus of the oculomotor complex or the lateral horns of the thoracic spinal cord.

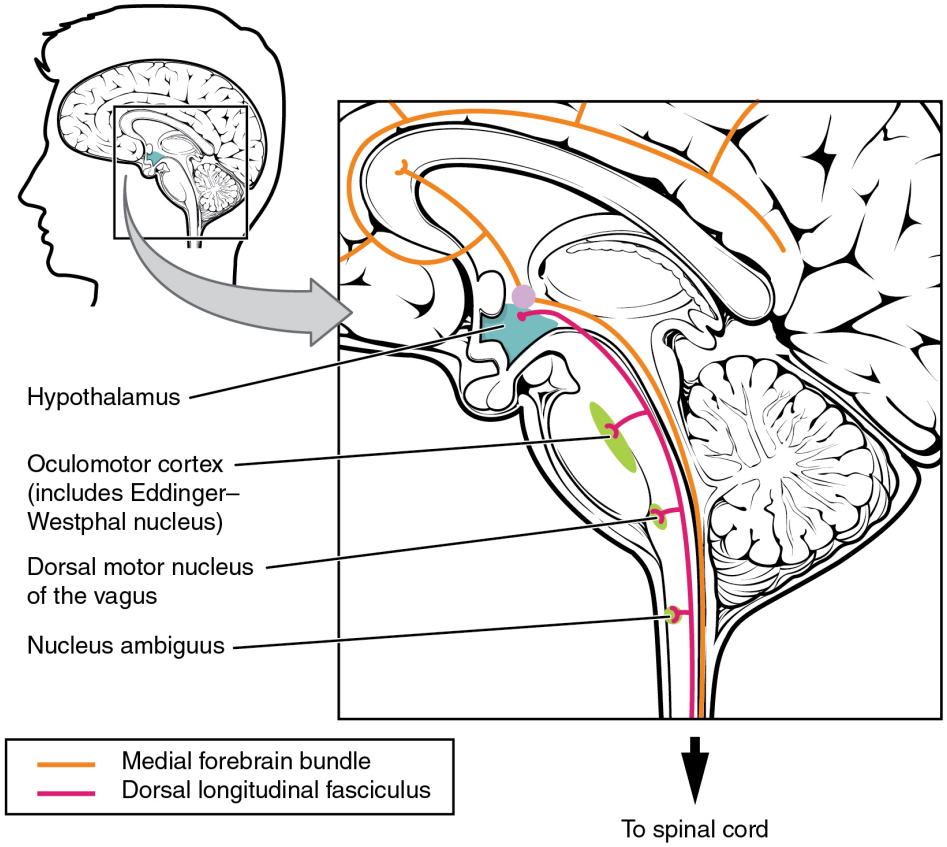


FIGURE 15.11 Fiber Tracts of the Central Autonomic System The hypothalamus is the source of most of the central control of autonomic function. It receives input from cerebral structures and projects to brain stem and spinal cord structures to regulate the balance of sympathetic and parasympathetic input to the organ systems of the body. The main pathways for this are the medial forebrain bundle and the dorsal longitudinal fasciculus.

These two tracts connect the hypothalamus with the major parasympathetic nuclei in the brain stem and the preganglionic (central) neurons of the thoracolumbar spinal cord. The hypothalamus also receives input from other areas of the forebrain through the medial forebrain bundle. The olfactory cortex, the septal nuclei of the basal forebrain, and the amygdala project into the hypothalamus through the medial forebrain bundle. These forebrain structures inform the hypothalamus about the state of the nervous system and can influence the regulatory processes of homeostasis. A good example of this is found in the amygdala, which is found beneath the cerebral cortex of the temporal lobe and plays a role in our ability to remember and feel emotions.

The Amygdala

The amygdala is a group of nuclei in the medial region of the temporal lobe that is part of the **limbic lobe** (Figure 15.12). The limbic lobe includes structures that are involved in emotional responses, as well as structures that contribute to memory function. The limbic lobe has strong connections with the hypothalamus and influences the

deeper, sweat glands to activate, and the digestive system to suspend activity. These are the same physiological changes associated with the fight-or-flight response, but there is nothing chasing you on that treadmill.

This is not a simple homeostatic mechanism at work because "maintaining the internal environment" would mean getting all those changes back to their set points. Instead, the sympathetic system has become active during exercise so that your body can cope with what is happening. A homeostatic mechanism is dealing with the conscious decision to push the body away from a resting state. The heart, actually, is moving away from its homeostatic set point. Without any input from the autonomic system, the heart would beat at approximately 100 bpm, and the parasympathetic system slows that down to the resting rate of approximately 70 bpm. But in the middle of a good workout, you should see your heart rate at 120–140 bpm. You could say that the body is stressed because of what you are doing to it. Homeostatic mechanisms are trying to keep blood pH in the normal range, or to keep body temperature under control, but those are in response to the choice to exercise.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/emotions) to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body's reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

15.4 Drugs that Affect the Autonomic System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- List the classes of pharmaceuticals that interact with the autonomic nervous system
- Differentiate between cholinergic and adrenergic compounds
- Differentiate between sympathomimetic and sympatholytic drugs
- Relate the consequences of nicotine abuse with respect to autonomic control of the cardiovascular system

An important way to understand the effects of native neurochemicals in the autonomic system is in considering the effects of pharmaceutical drugs. This can be considered in terms of how drugs change autonomic function. These effects will primarily be based on how drugs act at the receptors of the autonomic system neurochemistry. The signaling molecules of the nervous system interact with proteins in the cell membranes of various target cells. In fact, no effect can be attributed to just the signaling molecules themselves without considering the receptors. A chemical that the body produces to interact with those receptors is called an **endogenous chemical**, whereas a chemical introduced to the system from outside is an **exogenous chemical**. Exogenous chemicals may be of a natural origin, such as a plant extract, or they may be synthetically produced in a pharmaceutical laboratory.

Broad Autonomic Effects

One important drug that affects the autonomic system broadly is not a pharmaceutical therapeutic agent associated with the system. This drug is nicotine. The effects of nicotine on the autonomic nervous system are important in considering the role smoking can play in health.

All ganglionic neurons of the autonomic system, in both sympathetic and parasympathetic ganglia, are activated by ACh released from preganglionic fibers. The ACh receptors on these neurons are of the nicotinic type, meaning that they are ligand-gated ion channels. When the neurotransmitter released from the preganglionic fiber binds to the receptor protein, a channel opens to allow positive ions to cross the cell membrane. The result is depolarization of the ganglia. Nicotine acts as an ACh analog at these synapses, so when someone takes in the drug, it binds to these ACh receptors and activates the ganglionic neurons, causing them to depolarize.

Ganglia of both divisions are activated equally by the drug. For many target organs in the body, this results in no net change. The competing inputs to the system cancel each other out and nothing significant happens. For example, the sympathetic system will cause sphincters in the digestive tract to contract, limiting digestive propulsion, but the

particular adrenergic receptors and mimic norepinephrine at the synapses between sympathetic postganglionic fibers and their targets, or they increase the production and release of norepinephrine from postganglionic fibers. Also, to increase the effectiveness of adrenergic chemicals released from the fibers, some of these drugs may block the removal or reuptake of the neurotransmitter from the synapse.

A common sympathomimetic drug is phenylephrine, which is a common component of decongestants. It can also be used to dilate the pupil and to raise blood pressure. Phenylephrine is known as an α_1-adrenergic **agonist**, meaning that it binds to a specific adrenergic receptor, stimulating a response. In this role, phenylephrine will bind to the adrenergic receptors in bronchioles of the lungs and cause them to dilate. By opening these structures, accumulated mucus can be cleared out of the lower respiratory tract. Phenylephrine is often paired with other pharmaceuticals, such as analgesics, as in the "sinus" version of many over-the-counter drugs, such as Tylenol Sinus® or Excedrin Sinus®, or in expectorants for chest congestion such as in Robitussin CF®.

A related molecule, called pseudoephedrine, was much more commonly used in these applications than was phenylephrine, until the molecule became useful in the illicit production of amphetamines. Phenylephrine is not as effective as a drug because it can be partially broken down in the digestive tract before it is ever absorbed. Like the adrenergic agents, phenylephrine is effective in dilating the pupil, known as **mydriasis** (Figure 15.14). Phenylephrine is used during an eye exam in an ophthalmologist's or optometrist's office for this purpose. It can also be used to increase blood pressure in situations in which cardiac function is compromised, such as under anesthesia or during septic shock.

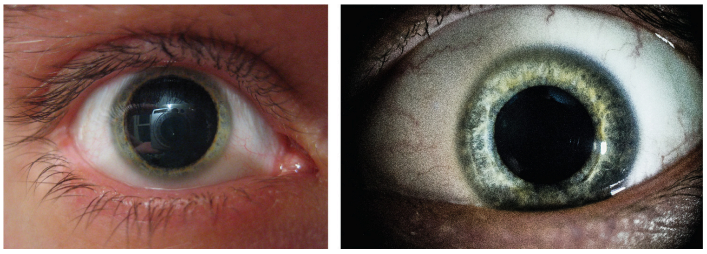


FIGURE 15.14 Mydriasis The sympathetic system causes pupillary dilation when norepinephrine binds to an adrenergic receptor in the radial fibers of the iris smooth muscle. Phenylephrine mimics this action by binding to the same receptor when drops are applied onto the surface of the eye in a doctor's office. (credit: Corey Theiss / Vulegenda/Wikimedia Commons)

Other drugs that enhance adrenergic function are not associated with therapeutic uses, but affect the functions of the sympathetic system in a similar fashion. Cocaine primarily interferes with the uptake of dopamine at the synapse and can also increase adrenergic function. Caffeine is an antagonist to a different neurotransmitter receptor, called the adenosine receptor. Adenosine will suppress adrenergic activity, specifically the release of norepinephrine at synapses, so caffeine indirectly increases adrenergic activity. There is some evidence that caffeine can aid in the therapeutic use of drugs, perhaps by potentiating (increasing) sympathetic function, as is suggested by the inclusion of caffeine in over-the-counter analgesics such as Excedrin®.

Sympatholytic Drugs

Drugs that interfere with sympathetic function are referred to as sympatholytic, or sympathoplegic, drugs. They primarily work as an **antagonist** to the adrenergic receptors. They block the ability of norepinephrine or epinephrine to bind to the receptors so that the effect is "cut" or "takes a blow," to refer to the endings "-lytic" and "-plegic," respectively. The various drugs of this class will be specific to α-adrenergic or β-adrenergic receptors, or to their receptor subtypes.

Possibly the most familiar type of sympatholytic drug are the β-blockers. These drugs are often used to treat cardiovascular disease because they block the β-receptors associated with vasoconstriction and cardioacceleration. By allowing blood vessels to dilate, or keeping heart rate from increasing, these drugs can improve cardiac function in a compromised system, such as for a person with congestive heart failure or who has previously suffered a heart attack. A couple of common versions of β-blockers are metoprolol, which specifically blocks the β_1-receptor, and propanolol, which nonspecifically blocks β-receptors. There are other drugs that are α-blockers and can affect the sympathetic system in a similar way.

Other uses for sympatholytic drugs are as antianxiety medications. A common example of this is clonidine, which is an α-agonist. The sympathetic system is tied to anxiety to the point that the sympathetic response can be referred

Sympathetic and Parasympathetic Effects of Different Drug Types

Drug type	Example(s)	Sympathetic effect	Parasympathetic effect	Overall result
Nicotinic agonists	Nicotine	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of norepinephrine onto the target organ	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of ACh onto the target organ	Most conflicting signals cancel each other out, but cardiovascular system is susceptible to hypertension and arrhythmias
Sympathomimetic drugs	Phenylephrine	Bind to adrenergic receptors or mimics sympathetic action in some other way	No effect	Increase sympathetic tone
Sympatholytic drugs	β-blockers such as propanolol or metoprolol; α-agonists such as clonidine	Block binding to adrenergic drug or decrease adrenergic signals	No effect	Increase parasympathetic tone
Parasymphatho-mimetics/ muscarinic agonists	Pilocarpine	No effect, except on sweat glands	Bind to muscarinic receptor, similar to ACh	Increase parasympathetic tone
Anticholinergics/ muscarinic antagonists	Atropine, scopolamine, dimenhydrinate	No effect	Block muscarinic receptors and parasympathetic function	Increase sympathetic tone

TABLE 15.2

Disorders of the...

Autonomic Nervous System

Approximately 33 percent of people experience a mild problem with motion sickness, whereas up to 66 percent experience motion sickness under extreme conditions, such as being on a tossing boat with no view of the horizon. Connections between regions in the brain stem and the autonomic system result in the symptoms of nausea, cold sweats, and vomiting.

The part of the brain responsible for vomiting, or emesis, is known as the area postrema. It is located next to the fourth ventricle and is not restricted by the blood–brain barrier, which allows it to respond to chemicals in the bloodstream—namely, toxins that will stimulate emesis. There are significant connections between this area, the solitary nucleus, and the dorsal motor nucleus of the vagus nerve. These autonomic system and nuclei connections are associated with the symptoms of motion sickness.

Motion sickness is the result of conflicting information from the visual and vestibular systems. If motion is

Key Terms

acetylcholine (ACh) neurotransmitter that binds at a motor end-plate to trigger depolarization

adrenal medulla interior portion of the adrenal (or suprarenal) gland that releases epinephrine and norepinephrine into the bloodstream as hormones

adrenergic synapse where norepinephrine is released, which binds to α- or β-adrenergic receptors

afferent branch component of a reflex arc that represents the input from a sensory neuron, for either a special or general sense

agonist any exogenous substance that binds to a receptor and produces a similar effect to the endogenous ligand

alpha (α)-adrenergic receptor one of the receptors to which epinephrine and norepinephrine bind, which comes in two subtypes: α_1 and α_2

antagonist any exogenous substance that binds to a receptor and produces an opposing effect to the endogenous ligand

anticholinergic drugs drugs that interrupt or reduce the function of the parasympathetic system

autonomic tone tendency of an organ system to be governed by one division of the autonomic nervous system over the other, such as heart rate being lowered by parasympathetic input at rest

baroreceptor mechanoreceptor that senses the stretch of blood vessels to indicate changes in blood pressure

beta (β)-adrenergic receptor one of the receptors to which epinephrine and norepinephrine bind, which comes in three subtypes: β_1, β_2, and β_3

cardiac accelerator nerves preganglionic sympathetic fibers that cause the heart rate to increase when the cardiovascular center in the medulla initiates a signal

cardiovascular center region in the medulla that controls the cardiovascular system through cardiac accelerator nerves and vasomotor nerves, which are components of the sympathetic division of the autonomic nervous system

celiac ganglion one of the collateral ganglia of the sympathetic system that projects to the digestive system

central neuron specifically referring to the cell body of a neuron in the autonomic system that is located in the central nervous system, specifically the lateral horn of the spinal cord or a brain stem nucleus

cholinergic synapse at which acetylcholine is released and binds to the nicotinic or muscarinic receptor

chromaffin cells neuroendocrine cells of the adrenal medulla that release epinephrine and norepinephrine into the bloodstream as part of sympathetic system activity

ciliary ganglion one of the terminal ganglia of the parasympathetic system, located in the posterior orbit, axons from which project to the iris

collateral ganglia ganglia outside of the sympathetic chain that are targets of sympathetic preganglionic fibers, which are the celiac, inferior mesenteric, and superior mesenteric ganglia

craniosacral system alternate name for the parasympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in brain-stem nuclei and the lateral horn of the sacral spinal cord; also referred to as craniosacral outflow

dorsal longitudinal fasciculus major output pathway of the hypothalamus that descends through the gray matter of the brain stem and into the spinal cord

dorsal nucleus of the vagus nerve location of parasympathetic neurons that project through the vagus nerve to terminal ganglia in the thoracic and abdominal cavities

Edinger–Westphal nucleus location of parasympathetic neurons that project to the ciliary ganglion

efferent branch component of a reflex arc that represents the output, with the target being an effector, such as muscle or glandular tissue

endogenous describes substance made in the human body

endogenous chemical substance produced and released within the body to interact with a receptor protein

epinephrine signaling molecule released from the adrenal medulla into the bloodstream as part of the sympathetic response

exogenous describes substance made outside of the human body

exogenous chemical substance from a source outside the body, whether it be another organism such as a plant or from the synthetic processes of a laboratory, that binds to a transmembrane receptor protein

fight-or-flight response set of responses induced by sympathetic activity that lead to either fleeing a threat or standing up to it, which in the modern world is often associated with anxious feelings

G protein–coupled receptor membrane protein complex that consists of a receptor protein that binds to a signaling molecule—a G protein—that is

response

sympatholytic drug drug that interrupts, or "lyses," the function of the sympathetic system

sympathomimetic drug drug that enhances or mimics the function of the sympathetic system

target effector organ, tissue, or gland that will respond to the control of an autonomic or somatic or endocrine signal

terminal ganglia ganglia of the parasympathetic division of the autonomic system, which are located near or within the target effector, the latter also known as intramural ganglia

thoracolumbar system alternate name for the sympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in the lateral horn of the thoracic and upper lumbar spinal cord

varicosity structure of some autonomic connections that is not a typical synaptic end bulb, but a string of swellings along the length of a fiber that makes a network of connections with the target effector

vasomotor nerves preganglionic sympathetic fibers that cause the constriction of blood vessels in response to signals from the cardiovascular center

visceral reflex reflex involving an internal organ as the effector, under the control of the autonomic nervous system

white rami communicantes (singular = ramus communicans) myelinated structures that provide a short connection from a sympathetic chain ganglion to the spinal nerve that contains the preganglionic sympathetic fiber

Chapter Review

15.1 Divisions of the Autonomic Nervous System

The primary responsibilities of the autonomic nervous system are to regulate homeostatic mechanisms in the body, which is also part of what the endocrine system does. The key to understanding the autonomic system is to explore the response pathways—the output of the nervous system. The way we respond to the world around us, to manage the internal environment on the basis of the external environment, is divided between two parts of the autonomic nervous system. The sympathetic division responds to threats and produces a readiness to confront the threat or to run away: the fight-or-flight response. The parasympathetic division plays the opposite role. When the external environment does not present any immediate danger, a restful mode descends on the body, and the digestive system is more active.

The sympathetic output of the nervous system originates out of the lateral horn of the thoracolumbar spinal cord. An axon from one of these central neurons projects by way of the ventral spinal nerve root and spinal nerve to a sympathetic ganglion, either in the sympathetic chain ganglia or one of the collateral locations, where it synapses on a ganglionic neuron. These preganglionic fibers release ACh, which excites the ganglionic neuron through the nicotinic receptor. The axon from the ganglionic neuron—the postganglionic fiber—then projects to a target effector where it will release norepinephrine to bind to an adrenergic receptor, causing a change in the physiology of that organ in keeping with the broad, divergent sympathetic response. The postganglionic connections to sweat glands in the skin and blood vessels supplying skeletal muscle are, however, exceptions; those fibers release ACh onto muscarinic receptors. The sympathetic system has a specialized preganglionic connection to the adrenal medulla that causes epinephrine and norepinephrine to be released into the bloodstream rather than exciting a neuron that contacts an organ directly. This hormonal component means that the sympathetic chemical signal can spread throughout the body very quickly and affect many organ systems at once.

The parasympathetic output is based in the brain stem and sacral spinal cord. Neurons from particular nuclei in the brain stem or from the lateral horn of the sacral spinal cord (preganglionic neurons) project to terminal (intramural) ganglia located close to or within the wall of target effectors. These preganglionic fibers also release ACh onto nicotinic receptors to excite the ganglionic neurons. The postganglionic fibers then contact the target tissues within the organ to release ACh, which binds to muscarinic receptors to induce rest-and-digest responses.

Signaling molecules utilized by the autonomic nervous system are released from axons and can be considered as either neurotransmitters (when they directly interact with the effector) or as hormones (when they are released into the bloodstream). The same molecule, such as norepinephrine, could be considered either a neurotransmitter or a hormone on the basis of whether it is released from a postganglionic sympathetic axon or from the adrenal gland. The synapses in the autonomic system are not always the typical type of connection first described in the neuromuscular junction. Instead of having synaptic end bulbs at the very end of an axonal fiber, they may have

increase in blood pressure. Also, the influence that the autonomic system has on the heart is not the same as for other systems. Other organs have smooth muscle or glandular tissue that is activated or inhibited by the autonomic system. Cardiac muscle is intrinsically active and is modulated by the autonomic system. The contradictory signals do not just cancel each other out, they alter the regularity of the heart rate and can cause arrhythmias. Both hypertension and arrhythmias are risk factors for heart disease.

Other drugs affect one division of the autonomic system or the other. The sympathetic system is affected by drugs that mimic the actions of adrenergic molecules (norepinephrine and epinephrine) and are called sympathomimetic drugs. Drugs such as phenylephrine bind to the adrenergic receptors and stimulate target organs just as sympathetic activity would. Other drugs are sympatholytic because they block adrenergic activity and cancel the sympathetic influence on the target organ. Drugs that act on the parasympathetic system also work by either enhancing the postganglionic signal or blocking it. A muscarinic agonist (or parasympathomimetic drug) acts just like ACh released by the parasympathetic postganglionic fiber. Anticholinergic drugs block muscarinic receptors, suppressing parasympathetic interaction with the organ.

Interactive Link Questions

1. Watch this video (http://openstax.org/l/fightflight) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?
2. Watch this video (http://openstax.org/l/nervsystem1) to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?
3. Read this article (http://openstax.org/l/strokespell) to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?
4. Watch this video (http://openstax.org/l/pupillary) to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?
5. Watch this video (http://openstax.org/l/emotions) to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body's reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

18. Which nerve projects to the hypothalamus to indicate the level of light stimuli in the retina?
   a. glossopharyngeal
   b. oculomotor
   c. optic
   d. vagus

19. What region of the limbic lobe is responsible for generating stress responses via the hypothalamus?
   a. hippocampus
   b. amygdala
   c. mammillary bodies
   d. prefrontal cortex

20. What is another name for the preganglionic sympathetic fibers that project to the heart?
   a. solitary tract
   b. vasomotor nerve
   c. vagus nerve
   d. cardiac accelerator nerve

21. What central fiber tract connects forebrain and brain stem structures with the hypothalamus?
   a. cardiac accelerator nerve
   b. medial forebrain bundle
   c. dorsal longitudinal fasciculus
   d. corticospinal tract

22. A drug that affects both divisions of the autonomic system is going to bind to, or block, which type of neurotransmitter receptor?
   a. nicotinic
   b. muscarinic
   c. α-adrenergic
   d. β-adrenergic

23. A drug is called an agonist if it _____.
   a. blocks a receptor
   b. interferes with neurotransmitter reuptake
   c. acts like the endogenous neurotransmitter by binding to its receptor
   d. blocks the voltage-gated calcium ion channel

24. Which type of drug would be an antidote to atropine poisoning?
   a. nicotinic agonist
   b. anticholinergic
   c. muscarinic agonist
   d. α-blocker

25. Which kind of drug would have anti-anxiety effects?
   a. nicotinic agonist
   b. anticholinergic
   c. muscarinic agonist
   d. α-blocker

26. Which type of drug could be used to treat asthma by opening airways wider?
   a. sympatholytic drug
   b. sympathomimetic drug
   c. anticholinergic drug
   d. parasympathomimetic drug

Critical Thinking Questions

27. In the context of a lioness hunting on the savannah, why would the sympathetic system *not* activate the digestive system?

28. A target effector, such as the heart, receives input from the sympathetic and parasympathetic systems. What is the actual difference between the sympathetic and parasympathetic divisions at the level of those connections (i.e., at the synapse)?

29. Damage to internal organs will present as pain associated with a particular surface area of the body. Why would something like irritation to the diaphragm, which is between the thoracic and abdominal cavities, feel like pain in the shoulder or neck?

30. Medical practice is paying more attention to the autonomic system in considering disease states. Why would autonomic tone be important in considering cardiovascular disease?

31. Horner's syndrome is a condition that presents with changes in one eye, such as pupillary constriction and dropping of eyelids, as well as decreased sweating in the face. Why could a tumor in the thoracic cavity have an effect on these autonomic functions?

32. The cardiovascular center is responsible for regulating the heart and blood vessels through homeostatic mechanisms. What tone does each component of the cardiovascular system have? What connections does the cardiovascular center invoke to keep these two systems in their resting tone?

nervous tissue, but indications of different specializations within the nervous tissue. However, not all nervous tissue performs the same function. Furthermore, specific functions are not wholly localized to individual brain structures in the way that other bodily functions occur strictly within specific organs. In the CNS, we must consider the connections between cells over broad areas, not just the function of cells in one particular nucleus or region. In a broad sense, the nervous system is responsible for the majority of electrochemical signaling in the body, but the use of those signals is different in various regions.

The nervous system is made up of the brain and spinal cord as the central organs, and the ganglia and nerves as organs in the periphery. The brain and spinal cord can be thought of as a collection of smaller organs, most of which would be the nuclei (such as the oculomotor nuclei), but white matter structures play an important role (such as the corpus callosum). Studying the nervous system requires an understanding of the varied physiology of the nervous system. For example, the hypothalamus plays a very different role than the visual cortex. The neurological exam provides a way to elicit behavior that represents those varied functions.

16.1 Overview of the Neurological Exam

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- List the major sections of the neurological exam
- Explain the connection between location and function in the nervous system
- Explain the benefit of a rapid assessment for neurological function in a clinical setting
- List the causes of neurological deficits
- Describe the different ischemic events in the nervous system

The **neurological exam** is a clinical assessment tool used to determine what specific parts of the CNS are affected by damage or disease. It can be performed in a short time—sometimes as quickly as 5 minutes—to establish neurological function. In the emergency department, this rapid assessment can make the difference with respect to proper treatment and the extent of recovery that is possible.

The exam is a series of subtests separated into five major sections. The first of these is the **mental status exam**, which assesses the higher cognitive functions such as memory, orientation, and language. Then there is the **cranial nerve exam**, which tests the function of the 12 cranial nerves and, therefore, the central and peripheral structures associated with them. The cranial nerve exam tests the sensory and motor functions of each of the nerves, as applicable. Two major sections, the **sensory exam** and the **motor exam**, test the sensory and motor functions associated with spinal nerves. Finally, the **coordination exam** tests the ability to perform complex and coordinated movements. The **gait exam**, which is often considered a sixth major exam, specifically assesses the motor function of walking and can be considered part of the coordination exam because walking is a coordinated movement.

Neuroanatomy and the Neurological Exam

Localization of function is the concept that circumscribed locations are responsible for specific functions. The neurological exam highlights this relationship. For example, the cognitive functions that are assessed in the mental status exam are based on functions in the cerebrum, mostly in the cerebral cortex. Several of the subtests examine language function. Deficits in neurological function uncovered by these examinations usually point to damage to the left cerebral cortex. In the majority of individuals, language function is localized to the left hemisphere between the superior temporal lobe and the posterior frontal lobe, including the intervening connections through the inferior parietal lobe.

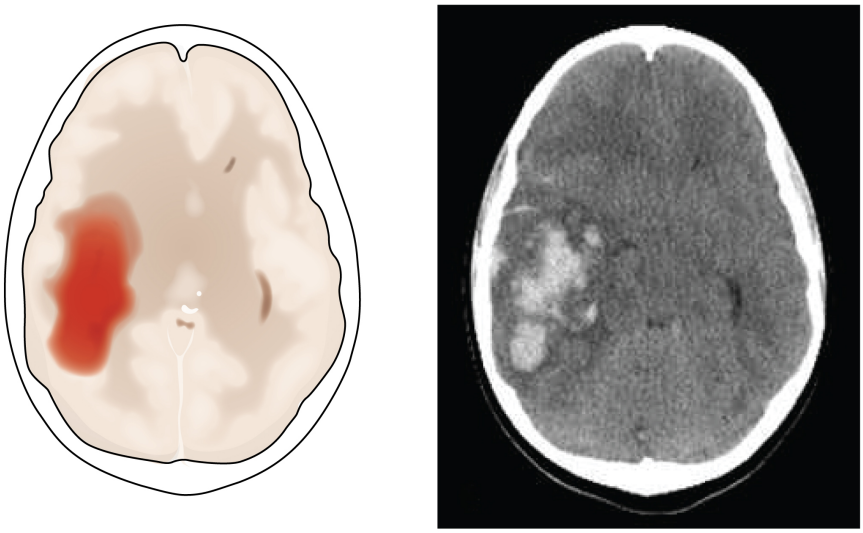
The five major sections of the neurological exam are related to the major regions of the CNS (Figure 16.2). The mental status exam assesses functions related to the cerebrum. The cranial nerve exam is for the nerves that connect to the diencephalon and brain stem (as well as the olfactory connections to the forebrain). The coordination exam and the related gait exam primarily assess the functions of the cerebellum. The motor and sensory exams are associated with the spinal cord and its connections through the spinal nerves.

permanent damage (cell death) could result within a few hours. The loss of blood flow to part of the brain is known as a **stroke**, or a cerebrovascular accident (CVA).

There are two main types of stroke, depending on how the blood supply is compromised: ischemic and hemorrhagic. An **ischemic stroke** is the loss of blood flow to an area because vessels are blocked or narrowed. This is often caused by an embolus, which may be a blood clot or fat deposit. Ischemia may also be the result of thickening of the blood vessel wall, or a drop in blood volume in the brain known as **hypovolemia**.

A related type of CVA is known as a **transient ischemic attack (TIA)**, which is similar to a stroke although it does not last as long. The diagnostic definition of a stroke includes effects that last at least 24 hours. Any stroke symptoms that are resolved within a 24-hour period because of restoration of adequate blood flow are classified as a TIA.

A **hemorrhagic stroke** is bleeding into the brain because of a damaged blood vessel. Accumulated blood fills a region of the cranial vault and presses against the tissue in the brain (Figure 16.3). Physical pressure on the brain can cause the loss of function, as well as the squeezing of local arteries resulting in compromised blood flow beyond the site of the hemorrhage. As blood pools in the nervous tissue and the vasculature is damaged, the blood-brain barrier can break down and allow additional fluid to accumulate in the region, which is known as **edema**.



(a) (b)

FIGURE 16.3 Hemorrhagic Stroke (a) A hemorrhage into the tissue of the cerebrum results in a large accumulation of blood with an additional edema in the adjacent tissue. The hemorrhagic area causes the entire brain to be disfigured as suggested here by the lateral ventricles being squeezed into the opposite hemisphere. (b) A CT scan shows an intraparenchymal hemorrhage within the parietal lobe. (credit b: James Heilman)

Whereas hemorrhagic stroke may involve bleeding into a large region of the CNS, such as into the deep white matter of a cerebral hemisphere, other events can cause widespread damage and loss of neurological functions. Infectious diseases can lead to loss of function throughout the CNS as components of nervous tissue, specifically astrocytes and microglia, react to the disease. Blunt force trauma, such as from a motor vehicle accident, can physically damage the CNS.

A class of disorders that affect the nervous system are the neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Creutzfeld–Jacob disease, multiple sclerosis (MS), and other disorders that are the result of nervous tissue degeneration. In diseases like Alzheimer's, Parkinson's, or ALS, neurons die; in diseases like MS, myelin is affected. Some of these disorders affect motor function, and others present with dementia. How patients with these disorders perform in the neurological exam varies, but is often broad in its effects, such as memory deficits that compromise many aspects of the mental status exam, or movement deficits that compromise aspects of the cranial nerve exam, the motor exam, or the coordination exam. The causes of these disorders are also varied. Some are the result of genetics, such as Huntington's disease, or the result of autoimmunity, such as MS; others are not entirely understood, such as Alzheimer's and Parkinson's diseases. Current research suggests that many of these diseases are related in how the degeneration takes place and may be treated by common therapies.

Functions of the Cerebral Cortex

The cerebrum is the seat of many of the higher mental functions, such as memory and learning, language, and conscious perception, which are the subjects of subtests of the mental status exam. The cerebral cortex is the thin layer of gray matter on the outside of the cerebrum. On average, it is approximately 2.55 mm thick and highly folded to fit within the limited space of the cranial vault. These higher functions are distributed across various regions of the cortex, and specific locations can be said to be responsible for particular functions. There is a limited set of regions, for example, that are involved in language function, and they can be subdivided on the basis of the particular part of language function that each governs.

The basis for parceling out areas of the cortex and attributing them to various functions has its root in pure anatomical underpinnings. The German neurologist and histologist Korbinian Brodmann, who made a careful study of the **cytoarchitecture** of the cerebrum around the turn of the nineteenth century, described approximately 50 regions of the cortex that differed enough from each other to be considered separate areas (Figure 16.4). Brodmann made preparations of many different regions of the cerebral cortex to view with a microscope. He compared the size, shape, and number of neurons to find anatomical differences in the various parts of the cerebral cortex. Continued investigation into these anatomical areas over the subsequent 100 or more years has demonstrated a strong correlation between the structures and the functions attributed to those structures. For example, the first three areas in Brodmann's list—which are in the postcentral gyrus—compose the primary somatosensory cortex. Within this area, finer separation can be made on the basis of the concept of the sensory homunculus, as well as the different submodalities of somatosensation such as touch, vibration, pain, temperature, or proprioception. Today, we more frequently refer to these regions by their function (i.e., primary sensory cortex) than by the number Brodmann assigned to them, but in some situations the use of Brodmann numbers persists.

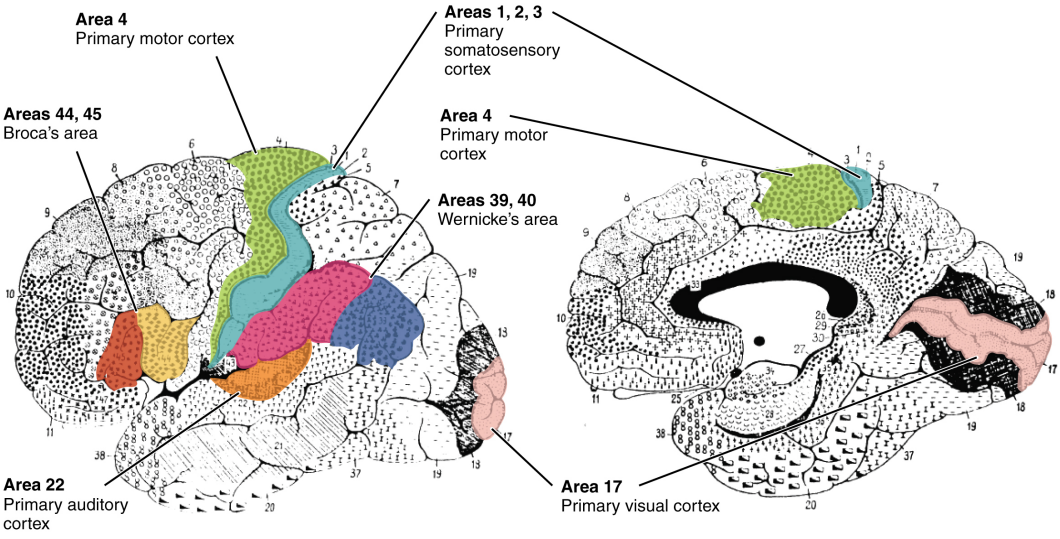


FIGURE 16.4 Brodmann's Areas of the Cerebral Cortex On the basis of cytoarchitecture, the anatomist Korbinian Brodmann described the extensive array of cortical regions, as illustrated in this figure. Subsequent investigations found that these areas corresponded very well to functional differences in the cerebral cortex. (credit: modification of work by "Looie496"/Wikimedia Commons, based on original work by Korvinian Brodmann)

Area 17, as Brodmann described it, is also known as the primary visual cortex. Adjacent to that are areas 18 and 19, which constitute subsequent regions of visual processing. Area 22 is the primary auditory cortex, and it is followed by area 23, which further processes auditory information. Area 4 is the primary motor cortex in the precentral gyrus, whereas area 6 is the premotor cortex. These areas suggest some specialization within the cortex for functional processing, both in sensory and motor regions. The fact that Brodmann's areas correlate so closely to functional localization in the cerebral cortex demonstrates the strong link between structure and function in these regions.

Areas 1, 2, 3, 4, 17, and 22 are each described as primary cortical areas. The adjoining regions are each referred to as association areas. Primary areas are where sensory information is initially received from the thalamus for

famous case of a man who had both medial temporal lobes removed to treat intractable epilepsy provided insight into the relationship between the structures of the brain and the function of memory.

Henry Molaison, who was referred to as patient HM when he was alive, had epilepsy localized to both of his medial temporal lobes. In 1953, a bilateral lobectomy was performed that alleviated the epilepsy but resulted in the inability for HM to form new memories—a condition called **anterograde amnesia**. HM was able to recall most events from before his surgery, although there was a partial loss of earlier memories, which is referred to as **retrograde amnesia**. HM became the subject of extensive studies into how memory works. What he was unable to do was form new memories of what happened to him, what are now called **episodic memory**. Episodic memory is autobiographical in nature, such as remembering riding a bicycle as a child around the neighborhood, as opposed to the **procedural memory** of how to ride a bike. HM also retained his **short-term memory**, such as what is tested by the three-word task described above. After a brief period, those memories would dissipate or decay and not be stored in the long-term because the medial temporal lobe structures were removed.

The difference in short-term, procedural, and episodic memory, as evidenced by patient HM, suggests that there are different parts of the brain responsible for those functions. The long-term storage of episodic memory requires the hippocampus and related medial temporal structures, and the location of those memories is in the multimodal integration areas of the cerebral cortex. However, short-term memory—also called working or active memory—is localized to the prefrontal lobe. Because patient HM had only lost his medial temporal lobe—and lost very little of his previous memories, and did not lose the ability to form new short-term memories—it was concluded that the function of the hippocampus, and adjacent structures in the medial temporal lobe, is to move (or consolidate) short-term memories (in the pre-frontal lobe) to long-term memory (in the temporal lobe).

The prefrontal cortex can also be tested for the ability to organize information. In one subtest of the mental status exam called set generation, the patient is asked to generate a list of words that all start with the same letter, but not to include proper nouns or names. The expectation is that a person can generate such a list of at least 10 words within 1 minute. Many people can likely do this much more quickly, but the standard separates the accepted normal from those with compromised prefrontal cortices.

INTERACTIVE LINK

Read this article (http://openstax.org/l/3word) to learn about a young man who texts his fiancée in a panic as he finds that he is having trouble remembering things. At the hospital, a neurologist administers the mental status exam, which is mostly normal except for the three-word recall test. The young man could not recall them even 30 seconds after hearing them and repeating them back to the doctor. An undiscovered mass in the mediastinum region was found to be Hodgkin's lymphoma, a type of cancer that affects the immune system and likely caused antibodies to attack the nervous system. The patient eventually regained his ability to remember, though the events in the hospital were always elusive. Considering that the effects on memory were temporary, but resulted in the loss of the specific events of the hospital stay, what regions of the brain were likely to have been affected by the antibodies and what type of memory does that represent?

Language and Speech

Language is, arguably, a very human aspect of neurological function. There are certainly strides being made in understanding communication in other species, but much of what makes the human experience seemingly unique is its basis in language. Any understanding of our species is necessarily reflective, as suggested by the question "What am I?" And the fundamental answer to this question is suggested by the famous quote by René Descartes: "Cogito Ergo Sum" (translated from Latin as "I think, therefore I am"). Formulating an understanding of yourself is largely describing who you are to yourself. It is a confusing topic to delve into, but language is certainly at the core of what it means to be self-aware.

The neurological exam has two specific subtests that address language. One measures the ability of the patient to understand language by asking them to follow a set of instructions to perform an action, such as "touch your right finger to your left elbow and then to your right knee." Another subtest assesses the fluency and coherency of language by having the patient generate descriptions of objects or scenes depicted in drawings, and by reciting sentences or explaining a written passage. Language, however, is important in so many ways in the neurological exam. The patient needs to know what to do, whether it is as simple as explaining how the knee-jerk reflex is going

The second subtest for sensory perception is **gnosis**, which involves two tasks. The first task, known as **stereognosis**, involves the naming of objects strictly on the basis of the somatosensory information that comes from manipulating them. The patient keeps their eyes closed and is given a common object, such as a coin, that they have to identify. The patient should be able to indicate the particular type of coin, such as a dime versus a penny, or a nickel versus a quarter, on the basis of the sensory cues involved. For example, the size, thickness, or weight of the coin may be an indication, or to differentiate the pairs of coins suggested here, the smooth or corrugated edge of the coin will correspond to the particular denomination. The second task, **graphesthesia**, is to recognize numbers or letters written on the palm of the hand with a dull pointer, such as a pen cap.

Praxis and gnosis are related to the conscious perception and cortical processing of sensory information. Being able to transform verbal commands into a sequence of motor responses, or to manipulate and recognize a common object and associate it with a name for that object. Both subtests have language components because language function is integral to these functions. The relationship between the words that describe actions, or the nouns that represent objects, and the cerebral location of these concepts is suggested to be localized to particular cortical areas. Certain aphasias can be characterized by a deficit of verbs or nouns, known as V impairment or N impairment, or may be classified as V–N dissociation. Patients have difficulty using one type of word over the other. To describe what is happening in a photograph as part of the expressive language subtest, a patient will use active- or image-based language. The lack of one or the other of these components of language can relate to the ability to use verbs or nouns. Damage to the region at which the frontal and temporal lobes meet, including the region known as the insula, is associated with V impairment; damage to the middle and inferior temporal lobe is associated with N impairment.

Judgment and Abstract Reasoning

Planning and producing responses requires an ability to make sense of the world around us. Making judgments and reasoning in the abstract are necessary to produce movements as part of larger responses. For example, when your alarm goes off, do you hit the snooze button or jump out of bed? Is 10 extra minutes in bed worth the extra rush to get ready for your day? Will hitting the snooze button multiple times lead to feeling more rested or result in a panic as you run late? How you mentally process these questions can affect your whole day.

The prefrontal cortex is responsible for the functions responsible for planning and making decisions. In the mental status exam, the subtest that assesses judgment and reasoning is directed at three aspects of frontal lobe function. First, the examiner asks questions about problem solving, such as “If you see a house on fire, what would you do?” The patient is also asked to interpret common proverbs, such as “Don’t look a gift horse in the mouth.” Additionally, pairs of words are compared for similarities, such as apple and orange, or lamp and cabinet.

The prefrontal cortex is composed of the regions of the frontal lobe that are not directly related to specific motor functions. The most posterior region of the frontal lobe, the precentral gyrus, is the primary motor cortex. Anterior to that are the premotor cortex, Broca’s area, and the frontal eye fields, which are all related to planning certain types of movements. Anterior to what could be described as motor association areas are the regions of the prefrontal cortex. They are the regions in which judgment, abstract reasoning, and working memory are localized. The antecedents to planning certain movements are judging whether those movements should be made, as in the example of deciding whether to hit the snooze button.

To an extent, the prefrontal cortex may be related to personality. The neurological exam does not necessarily assess personality, but it can be within the realm of neurology or psychiatry. A clinical situation that suggests this link between the prefrontal cortex and personality comes from the story of Phineas Gage, the railroad worker from the mid-1800s who had a metal spike impale his prefrontal cortex. There are suggestions that the steel rod led to changes in his personality. A man who was a quiet, dependable railroad worker became a raucous, irritable drunkard. Later anecdotal evidence from his life suggests that he was able to support himself, although he had to relocate and take on a different career as a stagecoach driver.

A psychiatric practice to deal with various disorders was the prefrontal lobotomy. This procedure was common in the 1940s and early 1950s, until antipsychotic drugs became available. The connections between the prefrontal cortex and other regions of the brain were severed. The disorders associated with this procedure included some aspects of what are now referred to as personality disorders, but also included mood disorders and psychoses. Depictions of lobotomies in popular media suggest a link between cutting the white matter of the prefrontal cortex

connect to muscles of the face, oral cavity, and pharynx, controlling facial expressions, mastication, swallowing, and speech. Four nerves make up the cranial component of the parasympathetic nervous system responsible for pupillary constriction, salivation, and the regulation of the organs of the thoracic and upper abdominal cavities. Finally, one nerve controls the muscles of the neck, assisting with spinal control of the movement of the head and neck.

The cranial nerve exam allows directed tests of forebrain and brain stem structures. The twelve cranial nerves serve the head and neck. The vagus nerve (cranial nerve X) has autonomic functions in the thoracic and superior abdominal cavities. The special senses are served through the cranial nerves, as well as the general senses of the head and neck. The movement of the eyes, face, tongue, throat, and neck are all under the control of cranial nerves. Preganglionic parasympathetic nerve fibers that control pupillary size, salivary glands, and the thoracic and upper abdominal viscera are found in four of the nerves. Tests of these functions can provide insight into damage to specific regions of the brain stem and may uncover deficits in adjacent regions.

Sensory Nerves

The olfactory, optic, and vestibulocochlear nerves (cranial nerves I, II, and VIII) are dedicated to four of the special senses: smell, vision, equilibrium, and hearing, respectively. Taste sensation is relayed to the brain stem through fibers of the facial and glossopharyngeal nerves. The trigeminal nerve is a mixed nerve that carries the general somatic senses from the head, similar to those coming through spinal nerves from the rest of the body.

Testing smell is straightforward, as common smells are presented to one nostril at a time. The patient should be able to recognize the smell of coffee or mint, indicating the proper functioning of the olfactory system. Loss of the sense of smell is called anosmia and can be lost following blunt trauma to the head or through aging. The short axons of the first cranial nerve regenerate on a regular basis. The neurons in the olfactory epithelium have a limited life span, and new cells grow to replace the ones that die off. The axons from these neurons grow back into the CNS by following the existing axons—representing one of the few examples of such growth in the mature nervous system. If all of the fibers are sheared when the brain moves within the cranium, such as in a motor vehicle accident, then no axons can find their way back to the olfactory bulb to re-establish connections. If the nerve is not completely severed, the anosmia may be temporary as new neurons can eventually reconnect.

Olfaction is not the pre-eminent sense, but its loss can be quite detrimental. The enjoyment of food is largely based on our sense of smell. Anosmia means that food will not seem to have the same taste, though the gustatory sense is intact, and food will often be described as being bland. However, the taste of food can be improved by adding ingredients (e.g., salt) that stimulate the gustatory sense.

Testing vision relies on the tests that are common in an optometry office. The **Snellen chart** (Figure 16.7) demonstrates visual acuity by presenting standard Roman letters in a variety of sizes. The result of this test is a rough generalization of the acuity of a person based on the normal accepted acuity, such that a letter that subtends a visual angle of 5 minutes of an arc at 20 feet can be seen. To have 20/60 vision, for example, means that the smallest letters that a person can see at a 20-foot distance could be seen by a person with normal acuity from 60 feet away. Testing the extent of the visual field means that the examiner can establish the boundaries of peripheral vision as simply as holding their hands out to either side and asking the patient when the fingers are no longer visible without moving the eyes to track them. If it is necessary, further tests can establish the perceptions in the visual fields. Physical inspection of the optic disk, or where the optic nerve emerges from the eye, can be accomplished by looking through the pupil with an ophthalmoscope.

Those fibers are conveying peripheral visual information to the opposite side of the brain, so the patient will experience "tunnel vision"—meaning that only the central visual field will be perceived.

The vestibulocochlear nerve (CN VIII) carries both equilibrium and auditory sensations from the inner ear to the medulla. Though the two senses are not directly related, anatomy is mirrored in the two systems. Problems with balance, such as vertigo, and deficits in hearing may both point to problems with the inner ear. Within the petrous region of the temporal bone is the bony labyrinth of the inner ear. The vestibule is the portion for equilibrium, composed of the utricle, saccule, and the three semicircular canals. The cochlea is responsible for transducing sound waves into a neural signal. The sensory nerves from these two structures travel side-by-side as the vestibulocochlear nerve, though they are really separate divisions. They both emerge from the inner ear, pass through the internal auditory meatus, and synapse in nuclei of the superior medulla. Though they are part of distinct sensory systems, the vestibular nuclei and the cochlear nuclei are close neighbors with adjacent inputs. Deficits in one or both systems could occur from damage that encompasses structures close to both. Damage to structures near the two nuclei can result in deficits to one or both systems.

Balance or hearing deficits may be the result of damage to the middle or inner ear structures. Ménière's disease is a disorder that can affect both equilibrium and audition in a variety of ways. The patient can suffer from vertigo, a low-frequency ringing in the ears, or a loss of hearing. From patient to patient, the exact presentation of the disease can be different. Additionally, within a single patient, the symptoms and signs may change as the disease progresses. Use of the neurological exam subtests for the vestibulocochlear nerve illuminates the changes a patient may go through. The disease appears to be the result of accumulation, or over-production, of fluid in the inner ear, in either the vestibule or cochlea.

Tests of equilibrium are important for coordination and gait and are related to other aspects of the neurological exam. The vestibulo-ocular reflex involves the cranial nerves for gaze control. Balance and equilibrium, as tested by the Romberg test, are part of spinal and cerebellar processes and involved in those components of the neurological exam, as discussed later.

Hearing is tested by using a tuning fork in a couple of different ways. The **Rinne test** involves using a tuning fork to distinguish between **conductive hearing** and **sensorineural hearing**. Conductive hearing relies on vibrations being conducted through the ossicles of the middle ear. Sensorineural hearing is the transmission of sound stimuli through the neural components of the inner ear and cranial nerve. A vibrating tuning fork is placed on the mastoid process and the patient indicates when the sound produced from this is no longer present. Then the fork is immediately moved to just next to the ear canal so the sound travels through the air. If the sound is not heard through the ear, meaning the sound is conducted better through the temporal bone than through the ossicles, a conductive hearing deficit is present. The **Weber test** also uses a tuning fork to differentiate between conductive versus sensorineural hearing loss. In this test, the tuning fork is placed at the top of the skull, and the sound of the tuning fork reaches both inner ears by travelling through bone. In a healthy patient, the sound would appear equally loud in both ears. With unilateral conductive hearing loss, however, the tuning fork sounds louder in the ear with hearing loss. This is because the sound of the tuning fork has to compete with background noise coming from the outer ear, but in conductive hearing loss, the background noise is blocked in the damaged ear, allowing the tuning fork to sound relatively louder in that ear. With unilateral sensorineural hearing loss, however, damage to the cochlea or associated nervous tissue means that the tuning fork sounds quieter in that ear.

The trigeminal system of the head and neck is the equivalent of the ascending spinal cord systems of the dorsal column and the spinothalamic pathways. Somatosensation of the face is conveyed along the nerve to enter the brain stem at the level of the pons. Synapses of those axons, however, are distributed across nuclei found throughout the brain stem. The mesencephalic nucleus processes proprioceptive information of the face, which is the movement and position of facial muscles. It is the sensory component of the **jaw-jerk reflex**, a stretch reflex of the masseter muscle. The chief nucleus, located in the pons, receives information about light touch as well as proprioceptive information about the mandible, which are both relayed to the thalamus and, ultimately, to the postcentral gyrus of the parietal lobe. The spinal trigeminal nucleus, located in the medulla, receives information about crude touch, pain, and temperature to be relayed to the thalamus and cortex. Essentially, the projection through the chief nucleus is analogous to the dorsal column pathway for the body, and the projection through the spinal trigeminal nucleus is analogous to the spinothalamic pathway.

Subtests for the sensory component of the trigeminal system are the same as those for the sensory exam targeting

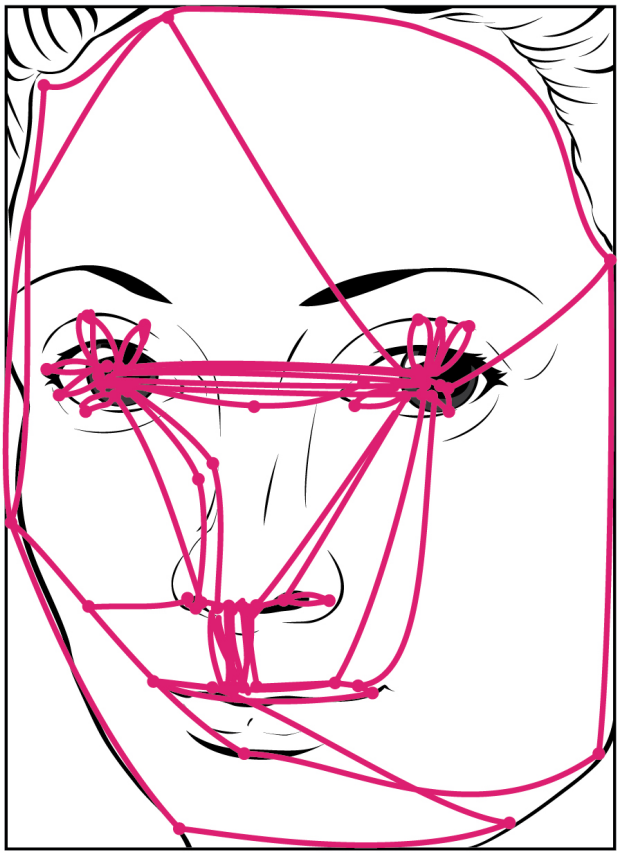


FIGURE 16.9 Saccadic Eye Movements Saccades are rapid, conjugate movements of the eyes to survey a complicated visual stimulus, or to follow a moving visual stimulus. This image represents the shifts in gaze typical of a person studying a face. Notice the concentration of gaze on the major features of the face and the large number of paths traced between the eyes or around the mouth.

Testing eye movement is simply a matter of having the patient track the tip of a pen as it is passed through the visual field. This may appear similar to testing visual field deficits related to the optic nerve, but the difference is that the patient is asked to not move the eyes while the examiner moves a stimulus into the peripheral visual field. Here, the extent of movement is the point of the test. The examiner is watching for conjugate movements representing proper function of the related nuclei and the MLF. Failure of one eye to abduct while the other adducts in a horizontal movement is referred to as **internuclear ophthalmoplegia**. When this occurs, the patient will experience **diplopia**, or double vision, as the two eyes are temporarily pointed at different stimuli. Diplopia is not restricted to failure of the lateral rectus, because any of the extraocular muscles may fail to move one eye in perfect conjugation with the other.

The final aspect of testing eye movements is to move the tip of the pen in toward the patient's face. As visual stimuli move closer to the face, the two medial recti muscles cause the eyes to move in the one nonconjugate movement that is part of gaze control. When the two eyes move to look at something closer to the face, they both adduct, which is referred to as **convergence**. To keep the stimulus in focus, the eye also needs to change the shape of the lens, which is controlled through the parasympathetic fibers of the oculomotor nerve. The change in focal power of the eye is referred to as **accommodation**. Accommodation ability changes with age; focusing on nearer objects, such as the written text of a book or on a computer screen, may require corrective lenses later in life. Coordination of the skeletal muscles for convergence and coordination of the smooth muscles of the ciliary body for accommodation are referred to as the **accommodation–convergence reflex**.

A crucial function of the cranial nerves is to keep visual stimuli centered on the fovea of the retina. The **vestibulo-ocular reflex (VOR)** coordinates all of the components (Figure 16.10), both sensory and motor, that make this possible. If the head rotates in one direction—for example, to the right—the horizontal pair of semicircular canals in the inner ear indicate the movement by increased activity on the right and decreased activity on the left. The information is sent to the abducens nuclei and oculomotor nuclei on either side to coordinate the lateral and medial rectus muscles. The left lateral rectus and right medial rectus muscles will contract, rotating the eyes in the

movement of the muscles around the fauces. The patient is asked to say “lah-kah-pah” or a similar set of alternating sounds while the examiner observes the movements of the soft palate and arches between the palate and tongue.

The facial and glossopharyngeal nerves are also responsible for the initiation of salivation. Neurons in the salivary nuclei of the medulla project through these two nerves as preganglionic fibers, and synapse in ganglia located in the head. The parasympathetic fibers of the facial nerve synapse in the pterygopalatine ganglion, which projects to the submandibular gland and sublingual gland. The parasympathetic fibers of the glossopharyngeal nerve synapse in the otic ganglion, which projects to the parotid gland. Salivation in response to food in the oral cavity is based on a visceral reflex arc within the facial or glossopharyngeal nerves. Other stimuli that stimulate salivation are coordinated through the hypothalamus, such as the smell and sight of food.

The hypoglossal nerve is the motor nerve that controls the muscles of the tongue, except for the palatoglossus muscle, which is controlled by the vagus nerve. There are two sets of muscles of the tongue. The **extrinsic muscles of the tongue** are connected to other structures, whereas the **intrinsic muscles of the tongue** are completely contained within the lingual tissues. While examining the oral cavity, movement of the tongue will indicate whether hypoglossal function is impaired. The test for hypoglossal function is the “stick out your tongue” part of the exam. The genioglossus muscle is responsible for protrusion of the tongue. If the hypoglossal nerves on both sides are working properly, then the tongue will stick straight out. If the nerve on one side has a deficit, the tongue will stick out to that side—pointing to the side with damage. Loss of function of the tongue can interfere with speech and swallowing. Additionally, because the location of the hypoglossal nerve and nucleus is near the cardiovascular center, inspiratory and expiratory areas for respiration, and the vagus nuclei that regulate digestive functions, a tongue that protrudes incorrectly can suggest damage in adjacent structures that have nothing to do with controlling the tongue.

INTERACTIVE LINK

Watch this short video (http://openstax.org/l/facialnerve) to see an examination of the facial nerve using some simple tests. The facial nerve controls the muscles of facial expression. Severe deficits will be obvious in watching someone use those muscles for normal control. One side of the face might not move like the other side. But directed tests, especially for contraction against resistance, require a formal testing of the muscles. The muscles of the upper and lower face need to be tested. The strength test in this video involves the patient squeezing her eyes shut and the examiner trying to pry her eyes open. Why does the examiner ask her to try a second time?

Motor Nerves of the Neck

The accessory nerve, also referred to as the spinal accessory nerve, innervates the sternocleidomastoid and trapezius muscles (Figure 16.11). When both the sternocleidomastoids contract, the head flexes forward; individually, they cause rotation to the opposite side. The trapezius can act as an antagonist, causing extension and hyperextension of the neck. These two superficial muscles are important for changing the position of the head. Both muscles also receive input from cervical spinal nerves. Along with the spinal accessory nerve, these nerves contribute to elevating the scapula and clavicle through the trapezius, which is tested by asking the patient to shrug both shoulders, and watching for asymmetry. For the sternocleidomastoid, those spinal nerves are primarily sensory projections, whereas the trapezius also has lateral insertions to the clavicle and scapula, and receives motor input from the spinal cord. Calling the nerve the spinal accessory nerve suggests that it is aiding the spinal nerves. Though that is not precisely how the name originated, it does help make the association between the function of this nerve in controlling these muscles and the role these muscles play in movements of the trunk or shoulders.

16.4 The Sensory and Motor Exams

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the arrangement of sensory and motor regions in the spinal cord
- Relate damage in the spinal cord to sensory or motor deficits
- Differentiate between upper motor neuron and lower motor neuron diseases
- Describe the clinical indications of common reflexes

Connections between the body and the CNS occur through the spinal cord. The cranial nerves connect the head and neck directly to the brain, but the spinal cord receives sensory input and sends motor commands out to the body through the spinal nerves. Whereas the brain develops into a complex series of nuclei and fiber tracts, the spinal cord remains relatively simple in its configuration (Figure 16.12). From the initial neural tube early in embryonic development, the spinal cord retains a tube-like structure with gray matter surrounding the small central canal and white matter on the surface in three columns. The dorsal, or posterior, horns of the gray matter are mainly devoted to sensory functions whereas the ventral, or anterior, and lateral horns are associated with motor functions. In the white matter, the dorsal column relays sensory information to the brain, and the anterior column is almost exclusively relaying motor commands to the ventral horn motor neurons. The lateral column, however, conveys both sensory and motor information between the spinal cord and brain.

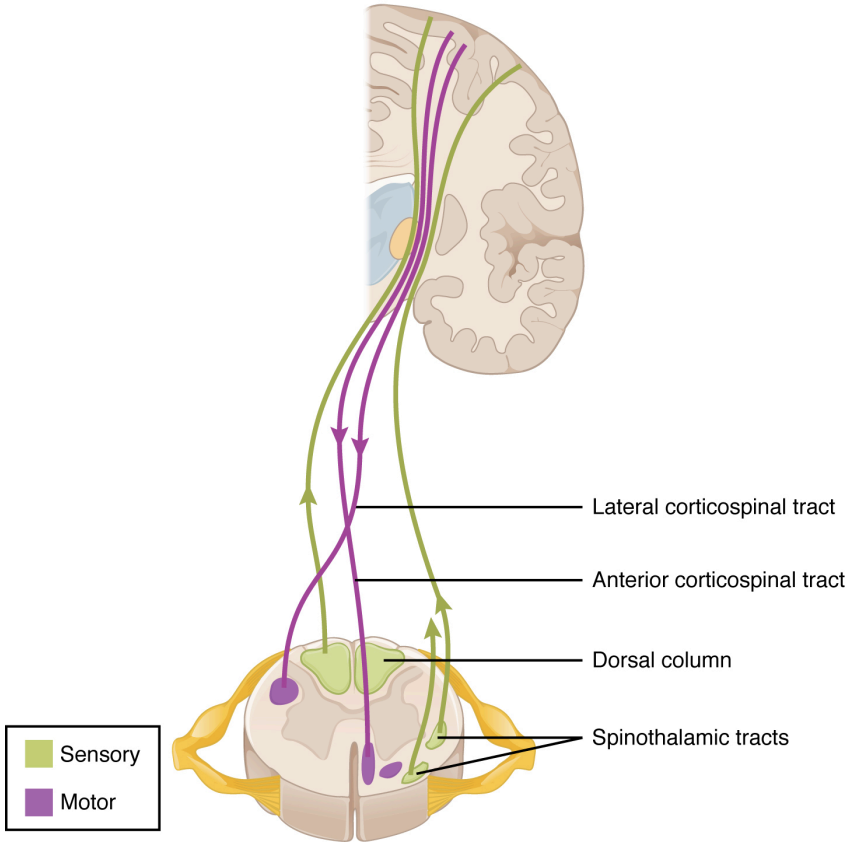


FIGURE 16.12 **Locations of Spinal Fiber Tracts**

Sensory Modalities and Location

The general senses are distributed throughout the body, relying on nervous tissue incorporated into various organs. Somatic senses are incorporated mostly into the skin, muscles, or tendons, whereas the visceral senses come from nervous tissue incorporated into the majority of organs such as the heart or stomach. The somatic senses are those that usually make up the conscious perception of the how the body interacts with the environment. The visceral senses are most often below the limit of conscious perception because they are involved in homeostatic regulation through the autonomic nervous system.

Using the cotton tip of the applicator, or even just a fingertip, the perception of tactile movement can be assessed as the stimulus is drawn across the skin for approximately 2–3 cm. The patient would be asked in what direction the stimulus is moving. All of these tests are repeated in distal and proximal locations and for different dermatomes to assess the spatial specificity of perception. The sense of position and motion, proprioception, is tested by moving the fingers or toes and asking the patient if they sense the movement. If the distal locations are not perceived, the test is repeated at increasingly proximal joints.

The various stimuli used to test sensory input assess the function of the major ascending tracts of the spinal cord. The dorsal column pathway conveys fine touch, vibration, and proprioceptive information, whereas the spinothalamic pathway primarily conveys pain and temperature. Testing these stimuli provides information about whether these two major ascending pathways are functioning properly. Within the spinal cord, the two systems are segregated. The dorsal column information ascends ipsilateral to the source of the stimulus and decussates in the medulla, whereas the spinothalamic pathway decussates at the level of entry and ascends contralaterally. The differing sensory stimuli are segregated in the spinal cord so that the various subtests for these stimuli can distinguish which ascending pathway may be damaged in certain situations.

Whereas the basic sensory stimuli are assessed in the subtests directed at each submodality of somatosensation, testing the ability to discriminate sensations is important. Pairing the light touch and pain subtests together makes it possible to compare the two submodalities at the same time, and therefore the two major ascending tracts at the same time. Mistaking painful stimuli for light touch, or vice versa, may point to errors in ascending projections, such as in a **hemisection** of the spinal cord that might come from a motor vehicle accident.

Another issue of sensory discrimination is not distinguishing between different submodalities, but rather location. The two-point discrimination subtest highlights the density of sensory endings, and therefore receptive fields in the skin. The sensitivity to fine touch, which can give indications of the texture and detailed shape of objects, is highest in the fingertips. To assess the limit of this sensitivity, two-point discrimination is measured by simultaneously touching the skin in two locations, such as could be accomplished with a pair of forceps. Specialized calipers for precisely measuring the distance between points are also available. The patient is asked to indicate whether one or two stimuli are present while keeping their eyes closed. The examiner will switch between using the two points and a single point as the stimulus. Failure to recognize two points may be an indication of a dorsal column pathway deficit.

Similar to two-point discrimination, but assessing laterality of perception, is double simultaneous stimulation. Two stimuli, such as the cotton tips of two applicators, are touched to the same position on both sides of the body. If one side is not perceived, this may indicate damage to the contralateral posterior parietal lobe. Because there is one of each pathway on either side of the spinal cord, they are not likely to interact. If none of the other subtests suggest particular deficits with the pathways, the deficit is likely to be in the cortex where conscious perception is based. The mental status exam contains subtests that assess other functions that are primarily localized to the parietal cortex, such as stereognosis and graphesthesia.

A final subtest of sensory perception that concentrates on the sense of proprioception is known as the **Romberg test**. The patient is asked to stand straight with feet together. Once the patient has achieved their balance in that position, they are asked to close their eyes. Without visual feedback that the body is in a vertical orientation relative to the surrounding environment, the patient must rely on the proprioceptive stimuli of joint and muscle position, as well as information from the inner ear, to maintain balance. This test can indicate deficits in dorsal column pathway proprioception, as well as problems with proprioceptive projections to the cerebellum through the **spinocerebellar tract**.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/2point) to see a quick demonstration of two-point discrimination. Touching a specialized caliper to the surface of the skin will measure the distance between two points that are perceived as distinct stimuli versus a single stimulus. The patient keeps their eyes closed while the examiner switches between using both points of the caliper or just one. The patient then must indicate whether one or two stimuli are in contact with the skin. Why is the distance between the caliper points closer on the fingertips as opposed to the palm of the hand? And what do you think the distance would be on the arm, or the shoulder?

INTERACTIVE LINK

Watch this video (http://openstax.org/l/reflextest) to see how to test reflexes in the abdomen. Testing reflexes of the trunk is not commonly performed in the neurological exam, but if findings suggest a problem with the thoracic segments of the spinal cord, a series of superficial reflexes of the abdomen can localize function to those segments. If contraction is not observed when the skin lateral to the umbilicus (belly button) is stimulated, what level of the spinal cord may be damaged?

Comparison of Upper and Lower Motor Neuron Damage

Many of the tests of motor function can indicate differences that will address whether damage to the motor system is in the upper or lower motor neurons. Signs that suggest a UMN lesion include muscle weakness, strong deep tendon reflexes, decreased control of movement or slowness, pronator drift, a positive Babinski sign, **spasticity**, and the **clasp-knife response**. Spasticity is an excess contraction in resistance to stretch. It can result in **hyperflexia**, which is when joints are overly flexed. The clasp-knife response occurs when the patient initially resists movement, but then releases, and the joint will quickly flex like a pocket knife closing.

A lesion on the LMN would result in paralysis, or at least partial loss of voluntary muscle control, which is known as **paresis**. The paralysis observed in LMN diseases is referred to as **flaccid paralysis**, referring to a complete or partial loss of muscle tone, in contrast to the loss of control in UMN lesions in which tone is retained and spasticity is exhibited. Other signs of an LMN lesion are **fibrillation**, **fasciculation**, and compromised or lost reflexes resulting from the denervation of the muscle fibers.

Disorders of the...

Spinal Cord

In certain situations, such as a motorcycle accident, only half of the spinal cord may be damaged in what is known as a hemisection. Forceful trauma to the trunk may cause ribs or vertebrae to fracture, and debris can crush or section through part of the spinal cord. The full section of a spinal cord would result in paraplegia, or loss of voluntary motor control of the lower body, as well as loss of sensations from that point down. A hemisection, however, will leave spinal cord tracts intact on one side. The resulting condition would be hemiplegia on the side of the trauma—one leg would be paralyzed. The sensory results are more complicated.

The ascending tracts in the spinal cord are segregated between the dorsal column and spinothalamic pathways. This means that the sensory deficits will be based on the particular sensory information each pathway conveys. Sensory discrimination between touch and painful stimuli will illustrate the difference in how these pathways divide these functions.

On the paralyzed leg, a patient will acknowledge painful stimuli, but not fine touch or proprioceptive sensations. On the functional leg, the opposite is true. The reason for this is that the dorsal column pathway ascends ipsilateral to the sensation, so it would be damaged the same way as the lateral corticospinal tract. The spinothalamic pathway decussates immediately upon entering the spinal cord and ascends contralateral to the source; it would therefore bypass the hemisection.

The motor system can indicate the loss of input to the ventral horn in the lumbar enlargement where motor neurons to the leg are found, but motor function in the trunk is less clear. The left and right anterior corticospinal tracts are directly adjacent to each other. The likelihood of trauma to the spinal cord resulting in a hemisection that affects one anterior column, but not the other, is very unlikely. Either the axial musculature will not be affected at all, or there will be bilateral losses in the trunk.

Sensory discrimination can pinpoint the level of damage in the spinal cord. Below the hemisection, pain stimuli will be perceived in the damaged side, but not fine touch. The opposite is true on the other side. The pain fibers on the side with motor function cross the midline in the spinal cord and ascend in the contralateral lateral column as far as the hemisection. The dorsal column will be intact ipsilateral to the source on the intact side and reach the brain for conscious perception. The trauma would be at the level just before sensory discrimination returns to normal, helping to pinpoint the trauma. Whereas imaging technology, like magnetic resonance

cerebellum, partially from the spinocerebellar tract, but also through fibers of the **inferior olive**. The MCP is part of the **cortico-ponto-cerebellar pathway** that connects the cerebral cortex with the cerebellum and preferentially targets the lateral regions of the cerebellum. It includes a copy of the motor commands sent from the precentral gyrus through the corticospinal tract, arising from collateral branches that synapse in the gray matter of the pons, along with input from other regions such as the visual cortex. The SCP is the major output of the cerebellum, divided between the **red nucleus** in the midbrain and the thalamus, which will return cerebellar processing to the motor cortex. These connections describe a circuit that compares motor commands and sensory feedback to generate a new output. These comparisons make it possible to coordinate movements. If the cerebral cortex sends a motor command to initiate walking, that command is copied by the pons and sent into the cerebellum through the MCP. Sensory feedback in the form of proprioception from the spinal cord, as well as vestibular sensations from the inner ear, enters through the ICP. If you take a step and begin to slip on the floor because it is wet, the output from the cerebellum—through the SCP—can correct for that and keep you balanced and moving. The red nucleus sends new motor commands to the spinal cord through the **rubrospinal tract**.

The cerebellum is divided into regions that are based on the particular functions and connections involved. The midline regions of the cerebellum, the **vermis** and **flocculonodular lobe**, are involved in comparing visual information, equilibrium, and proprioceptive feedback to maintain balance and coordinate movements such as walking, or **gait**, through the descending output of the red nucleus (Figure 16.15). The lateral hemispheres are primarily concerned with planning motor functions through frontal lobe inputs that are returned through the thalamic projections back to the premotor and motor cortices. Processing in the midline regions targets movements of the axial musculature, whereas the lateral regions target movements of the appendicular musculature. The vermis is referred to as the **spinocerebellum** because it primarily receives input from the dorsal columns and spinocerebellar pathways. The flocculonodular lobe is referred to as the **vestibulocerebellum** because of the vestibular projection into that region. Finally, the lateral cerebellum is referred to as the **cerebrocerebellum**, reflecting the significant input from the cerebral cortex through the cortico-ponto-cerebellar pathway.

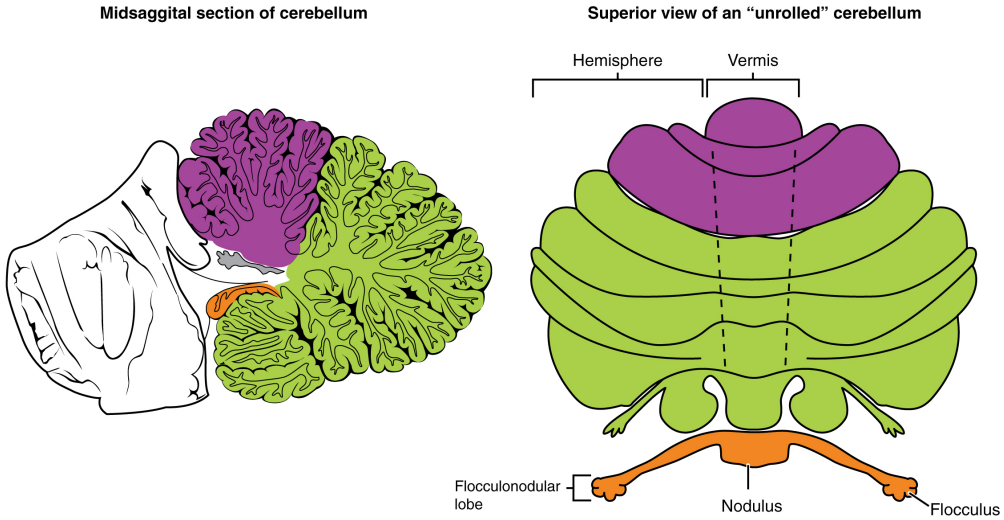


FIGURE 16.15 Major Regions of the Cerebellum The cerebellum can be divided into two basic regions: the midline and the hemispheres. The midline is composed of the vermis and the flocculonodular lobe, and the hemispheres are the lateral regions.

Coordination and Alternating Movement

Testing for cerebellar function is the basis of the coordination exam. The subtests target appendicular musculature, controlling the limbs, and axial musculature for posture and gait. The assessment of cerebellar function will depend on the normal functioning of other systems addressed in previous sections of the neurological exam. Motor control from the cerebrum, as well as sensory input from somatic, visual, and vestibular senses, are important to cerebellar function.

The subtests that address appendicular musculature, and therefore the lateral regions of the cerebellum, begin with a check for tremor. The patient extends their arms in front of them and holds the position. The examiner watches for the presence of tremors that would not be present if the muscles are relaxed. By pushing down on the arms in this position, the examiner can check for the rebound response, which is when the arms are automatically brought back

the head and neck, or MS. Alcohol intoxication or drugs such as ketamine cause ataxia, but it is often reversible. Mercury in fish can cause ataxia as well. Hereditary conditions can lead to degeneration of the cerebellum or spinal cord, as well as malformation of the brain, or the abnormal accumulation of copper seen in Wilson's disease.

INTERACTIVE LINK

Watch this short video (http://openstax.org/l/stationtest) to see a test for station. Station refers to the position a person adopts when they are standing still. The examiner would look for issues with balance, which coordinates proprioceptive, vestibular, and visual information in the cerebellum. To test the ability of a subject to maintain balance, asking them to stand or hop on one foot can be more demanding. The examiner may also push the subject to see if they can maintain balance. An abnormal finding in the test of station is if the feet are placed far apart. Why would a wide stance suggest problems with cerebellar function?

Everyday Connection

The Field Sobriety Test

The neurological exam has been described as a clinical tool throughout this chapter. It is also useful in other ways. A variation of the coordination exam is the Field Sobriety Test (FST) used to assess whether drivers are under the influence of alcohol. The cerebellum is crucial for coordinated movements such as keeping balance while walking, or moving appendicular musculature on the basis of proprioceptive feedback. The cerebellum is also very sensitive to ethanol, the particular type of alcohol found in beer, wine, and liquor.

Walking in a straight line involves comparing the motor command from the primary motor cortex to the proprioceptive and vestibular sensory feedback, as well as following the visual guide of the white line on the side of the road. When the cerebellum is compromised by alcohol, the cerebellum cannot coordinate these movements effectively, and maintaining balance becomes difficult.

Another common aspect of the FST is to have the driver extend their arms out wide and touch their fingertip to their nose, usually with their eyes closed. The point of this is to remove the visual feedback for the movement and force the driver to rely just on proprioceptive information about the movement and position of their fingertip relative to their nose. With eyes open, the corrections to the movement of the arm might be so small as to be hard to see, but proprioceptive feedback is not as immediate and broader movements of the arm will probably be needed, particularly if the cerebellum is affected by alcohol.

Reciting the alphabet backwards is not always a component of the FST, but its relationship to neurological function is interesting. There is a cognitive aspect to remembering how the alphabet goes and how to recite it backwards. That is actually a variation of the mental status subtest of repeating the months backwards. However, the cerebellum is important because speech production is a coordinated activity. The speech rapid alternating movement subtest is specifically using the consonant changes of "lah-kah-pah" to assess coordinated movements of the lips, tongue, pharynx, and palate. But the entire alphabet, especially in the nonrehearsed backwards order, pushes this type of coordinated movement quite far. It is related to the reason that speech becomes slurred when a person is intoxicated.

hypovolemia decrease in blood volume
inferior cerebellar peduncle (ICP) input to the cerebellum, largely from the inferior olive, that represents sensory feedback from the periphery
inferior olive large nucleus in the medulla that receives input from sensory systems and projects into the cerebellar cortex
internuclear ophthalmoplegia deficit of conjugate lateral gaze because the lateral rectus muscle of one eye does not contract resulting from damage to the abducens nerve or the MLF
intorsion medial rotation of the eye around its axis
intrinsic muscles of the tongue muscles that originate out of, and insert into, other tissues within the tongue and control the shape of the tongue
ischemic stroke disruption of blood flow to the brain because blood cannot flow through blood vessels as a result of a blockage or narrowing of the vessel
jaw-jerk reflex stretch reflex of the masseter muscle
localization of function principle that circumscribed anatomical locations are responsible for specific functions in an organ system
medial longitudinal fasciculus (MLF) fiber pathway that connects structures involved in the control of eye and head position, from the superior colliculus to the vestibular nuclei and cerebellum
mental status exam major section of the neurological exam that assesses cognitive functions of the cerebrum
middle cerebellar peduncle (MCP) large, white-matter bridge from the pons that constitutes the major input to the cerebellar cortex
motor exam major section of the neurological exam that assesses motor functions of the spinal cord and spinal nerves
neurological exam clinical assessment tool that can be used to quickly evaluate neurological function and determine if specific parts of the nervous system have been affected by damage or disease
paramedian pontine reticular formation (PPRF) region of the brain stem adjacent to the motor nuclei for gaze control that coordinates rapid, conjugate eye movements
paresis partial loss of, or impaired, voluntary muscle control
plantar reflex superficial reflex initiated by gentle stimulation of the sole of the foot
praxis in a neurological exam, the act of doing something using ready knowledge or skills in response to verbal instruction
procedural memory memory of how to perform a specific task
pronator drift sign of contralateral corticospinal lesion when the one arm will drift into a pronated position when held straight out with the palms facing upward
receptive aphasia loss of the ability to understand received language, such as what is spoken to the subject or given in written form
red nucleus nucleus in the midbrain that receives output from the cerebellum and projects onto the spinal cord in the rubrospinal tract
retrograde amnesia loss of memories before a particular event
Rinne test use of a tuning fork to test conductive hearing loss versus sensorineural hearing loss
Romberg test test of equilibrium that requires the patient to maintain a straight, upright posture without visual feedback of position
rubrospinal tract descending tract from the red nucleus of the midbrain that results in modification of ongoing motor programs
saccade small, rapid movement of the eyes used to locate and direct the fovea onto visual stimuli
sensorineural hearing hearing dependent on the transduction and propagation of auditory information through the neural components of the peripheral auditory structures
sensory exam major section of the neurological exam that assesses sensory functions of the spinal cord and spinal nerves
short-term memory capacity to retain information actively in the brain for a brief period of time
Snellen chart standardized arrangement of letters in decreasing size presented to a subject at a distance of 20 feet to test visual acuity
spasticity increased contraction of a muscle in response to resistance, often resulting in hyperflexia
spinocerebellar tract ascending fibers that carry proprioceptive input to the cerebellum used in maintaining balance and coordinated movement
spinocerebellum midline region of the cerebellum known as the vermis that receives proprioceptive input from the spinal cord
stereognosis perception of common objects placed in the hand solely on the basis of manipulation of that object in the hand
stroke (also, cerebrovascular accident (CVA)) loss of neurological function caused by an interruption of blood flow to a region of the central nervous system
superficial reflex reflexive contraction initiated by gentle stimulation of the skin
superior cerebellar peduncle (SCP) white-matter tract representing output of the cerebellum to the red nucleus of the midbrain
transient ischemic attack (TIA) temporary

face, and taste—separated between the anterior two-thirds of the tongue and the posterior one-third. Special senses are tested by presenting the particular stimuli to each receptive organ. General senses can be tested through sensory discrimination of touch versus painful stimuli.

The oculomotor, trochlear, and abducens nerves control the extraocular muscles and are connected by the medial longitudinal fasciculus to coordinate gaze. Testing conjugate gaze is as simple as having the patient follow a visual target, like a pen tip, through the visual field ending with an approach toward the face to test convergence and accommodation. Along with the vestibular functions of the eighth nerve, the vestibulo-ocular reflex stabilizes gaze during head movements by coordinating equilibrium sensations with the eye movement systems.

The trigeminal nerve controls the muscles of chewing, which are tested for stretch reflexes. Motor functions of the facial nerve are usually obvious if facial expressions are compromised, but can be tested by having the patient raise their eyebrows, smile, and frown. Movements of the tongue, soft palate, or superior pharynx can be observed directly while the patient swallows, while the gag reflex is elicited, or while the patient says repetitive consonant sounds. The motor control of the gag reflex is largely controlled by fibers in the vagus nerve and constitutes a test of that nerve because the parasympathetic functions of that nerve are involved in visceral regulation, such as regulating the heartbeat and digestion.

Movement of the head and neck using the sternocleidomastoid and trapezius muscles is controlled by the accessory nerve. Flexing of the neck and strength testing of those muscles reviews the function of that nerve.

16.4 The Sensory and Motor Exams

The sensory and motor exams assess function related to the spinal cord and the nerves connected to it. Sensory functions are associated with the dorsal regions of the spinal cord, whereas motor function is associated with the ventral side. Localizing damage to the spinal cord is related to assessments of the peripheral projections mapped to dermatomes.

Sensory tests address the various submodalities of the somatic senses: touch, temperature, vibration, pain, and proprioception. Results of the subtests can point to trauma in the spinal cord gray matter, white matter, or even in connections to the cerebral cortex.

Motor tests focus on the function of the muscles and the connections of the descending motor pathway. Muscle tone and strength are tested for upper and lower extremities. Input to the muscles comes from the descending cortical input of upper motor neurons and the direct innervation of lower motor neurons.

Reflexes can either be based on deep stimulation of tendons or superficial stimulation of the skin. The presence of reflexive contractions helps to differentiate motor disorders between the upper and lower motor neurons. The specific signs associated with motor disorders can establish the difference further, based on the type of paralysis, the state of muscle tone, and specific indicators such as pronator drift or the Babinski sign.

16.5 The Coordination and Gait Exams

The cerebellum is an important part of motor function in the nervous system. It apparently plays a role in procedural learning, which would include motor skills such as riding a bike or throwing a football. The basis for these roles is likely to be tied into the role the cerebellum plays as a comparator for voluntary movement.

The motor commands from the cerebral hemispheres travel along the corticospinal pathway, which passes through the pons. Collateral branches of these fibers synapse on neurons in the pons, which then project into the cerebellar cortex through the middle cerebellar peduncles. Ascending sensory feedback, entering through the inferior cerebellar peduncles, provides information about motor performance. The cerebellar cortex compares the command to the actual performance and can adjust the descending input to compensate for any mismatch. The output from deep cerebellar nuclei projects through the superior cerebellar peduncles to initiate descending signals from the red nucleus to the spinal cord.

The primary role of the cerebellum in relation to the spinal cord is through the spinocerebellum; it controls posture and gait with significant input from the vestibular system. Deficits in cerebellar function result in ataxias, or a specific kind of movement disorder. The root cause of the ataxia may be the sensory input—either the proprioceptive input from the spinal cord or the equilibrium input from the vestibular system, or direct damage to the cerebellum by stroke, trauma, hereditary factors, or toxins.

7. Watch this video (http://openstax.org/l/reflextest) to see how to test reflexes in the abdomen. Testing reflexes of the trunk is not commonly performed in the neurological exam, but if findings suggest a problem with the thoracic segments of the spinal cord, a series of superficial reflexes of the abdomen can localize function to those segments. If contraction is not observed when the skin lateral to the umbilicus (belly button) is stimulated, what level of the spinal cord may be damaged?

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Review Questions

9. Which major section of the neurological exam is *most likely* to reveal damage to the cerebellum?
a. cranial nerve exam
b. mental status exam
c. sensory exam
d. coordination exam

10. What function would *most likely* be affected by a restriction of a blood vessel in the cerebral cortex?
a. language
b. gait
c. facial expressions
d. knee-jerk reflex

11. Which major section of the neurological exam includes subtests that are sometimes considered a separate set of tests concerned with walking?
a. mental status exam
b. cranial nerve exam
c. coordination exam
d. sensory exam

12. Memory, emotional, language, and sensorimotor deficits together are *most likely* the result of what kind of damage?
a. stroke
b. developmental disorder
c. whiplash
d. gunshot wound

13. Where is language function localized in the majority of people?
a. cerebellum
b. right cerebral hemisphere
c. hippocampus
d. left cerebral hemisphere

14. Which of the following could be elements of cytoarchitecture, as related to Brodmann's microscopic studies of the cerebral cortex?
a. connections to the cerebellum
b. activation by visual stimuli
c. number of neurons per square millimeter
d. number of gyri or sulci

15. Which of the following could be a multimodal integrative area?
a. primary visual cortex
b. premotor cortex
c. hippocampus
d. Wernicke's area

16. Which is an example of episodic memory?
a. how to bake a cake
b. your last birthday party
c. how old you are
d. needing to wear an oven mitt to take a cake out of the oven

17. Which type of aphasia is more like hearing a foreign language spoken?
a. receptive aphasia
b. expressive aphasia
c. conductive aphasia
d. Broca's aphasia

18. What region of the cerebral cortex is associated with understanding language, both from another person and the language a person generates himself or herself?
a. medial temporal lobe
b. ventromedial prefrontal cortex
c. superior temporal gyrus
d. postcentral gyrus

Critical Thinking Questions

34. Why is a rapid assessment of neurological function important in an emergency situation?

35. How is the diagnostic category of TIA different from a stroke?

36. A patient's performance of the majority of the mental status exam subtests is in line with the expected norms, but the patient cannot repeat a string of numbers given by the examiner. What is a likely explanation?

37. A patient responds to the question "What is your name?" with a look of incomprehension. Which of the two major language areas is most likely affected and what is the name for that type of aphasia?

38. As a person ages, their ability to focus on near objects (accommodation) changes. If a person is already myopic (near-sighted), why would corrective lenses not be necessary to read a book or computer screen?

39. When a patient flexes their neck, the head tips to the right side. Also, their tongue sticks out slightly to the left when they try to stick it straight out. Where is the damage to the brain stem most likely located?

40. The location of somatosensation is based on the topographical map of sensory innervation. What does this mean?

41. Why are upper motor neuron lesions characterized by "spastic paralysis"?

42. Learning to ride a bike is a motor function dependent on the cerebellum. Why are the different regions of the cerebellum involved in this complex motor learning?

43. Alcohol intoxication can produce slurred speech. How is this related to cerebellar function?

homeostasis in the body.

Neural and Endocrine Signaling

The nervous system uses two types of intercellular communication—electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters such as serotonin or norepinephrine. Neurotransmitters act locally and rapidly. When an electrical signal in the form of an action potential arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap between a sending neuron and a receiving neuron or muscle cell). Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response. The target cell responds within milliseconds of receiving the chemical "message"; this response then ceases very quickly once the neural signaling ends. In this way, neural communication enables body functions that involve quick, brief actions, such as movement, sensation, and cognition.In contrast, the **endocrine system** uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the **hormone**—into the extracellular fluid. Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response. As a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones. For example, the hormones released when you are confronted with a dangerous or frightening situation, called the fight-or-flight response, occur by the release of adrenal hormones—epinephrine and norepinephrine—within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

INTERACTIVE LINK

Visit this link (http://openstax.org/l/hormonebind) to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?

In addition, endocrine signaling is typically less specific than neural signaling. The same hormone may play a role in a variety of different physiological processes depending on the target cells involved. For example, the hormone oxytocin promotes uterine contractions in people in labor. It is also important in breastfeeding, and may be involved in the sexual response and in feelings of emotional attachment in humans.

In general, the nervous system involves quick responses to rapid changes in the external environment, and the endocrine system is usually slower acting—taking care of the internal environment of the body, maintaining homeostasis, and controlling reproduction (Table 17.1). So how does the fight-or-flight response that was mentioned earlier happen so quickly if hormones are usually slower acting? It is because the two systems are connected. It is the fast action of the nervous system in response to the danger in the environment that stimulates the adrenal glands to secrete their hormones. As a result, the nervous system can cause rapid endocrine responses to keep up with sudden changes in both the external and internal environments when necessary.

Endocrine and Nervous Systems

	Endocrine system	Nervous system
Signaling mechanism(s)	Chemical	Chemical/electrical
Primary chemical signal	Hormones	Neurotransmitters
Distance traveled	Long or short	Always short

TABLE 17.1

and accessory ducts to the lumen of the small intestine.

Other Types of Chemical Signaling

In endocrine signaling, hormones secreted into the extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body. In contrast, autocrine signaling takes place within the same cell. An **autocrine** (auto- = "self") is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the province of the **paracrine**, also called a paracrine factor, which is a chemical that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways. Another example is the neurotransmitters of the nervous system, which act only locally within the synaptic cleft.



CAREER CONNECTION

Endocrinologist

Endocrinology is a specialty in the field of medicine that focuses on the treatment of endocrine system disorders. Endocrinologists—medical doctors who specialize in this field—are experts in treating diseases associated with hormonal systems, ranging from thyroid disease to diabetes mellitus. Endocrine surgeons treat endocrine disease through the removal, or resection, of the affected endocrine gland.

Patients who are referred to endocrinologists may have signs and symptoms or blood test results that suggest excessive or impaired functioning of an endocrine gland or endocrine cells. The endocrinologist may order additional blood tests to determine whether the patient's hormonal levels are abnormal, or they may stimulate or suppress the function of the suspect endocrine gland and then have blood taken for analysis. Treatment varies according to the diagnosis. Some endocrine disorders, such as type 2 diabetes, may respond to lifestyle changes such as modest weight loss, adoption of a healthy diet, and regular physical activity. Other disorders may require medication, such as hormone replacement, and routine monitoring by the endocrinologist. These include disorders of the pituitary gland that can affect growth and disorders of the thyroid gland that can result in a variety of metabolic problems.

Some patients experience health problems as a result of the normal decline in hormones that can accompany aging. These patients can consult with an endocrinologist to weigh the risks and benefits of hormone replacement therapy intended to boost their natural levels of reproductive hormones.

In addition to treating patients, endocrinologists may be involved in research to improve the understanding of endocrine system disorders and develop new treatments for these diseases.

17.2 Hormones

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the three major classes of hormones on the basis of chemical structure
- Compare and contrast intracellular and cell membrane hormone receptors
- Describe signaling pathways that involve cAMP and IP3
- Identify several factors that influence a target cell's response
- Discuss the role of feedback loops and humoral, hormonal, and neural stimuli in hormone control

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell's response. Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many

Endocrine gland	Associated hormones	Chemical class	Effect
Pancreas	Insulin	Protein	Reduces blood glucose levels
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of sex characteristics including a deeper voice, increased muscle mass, development of body hair, and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of sex characteristics including the development of adipose and breast tissue, and prepare the body for childbirth

TABLE 17.2

Types of Hormones

The hormones of the human body can be divided into two major groups on the basis of their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids (Figure 17.3). These chemical groups affect a hormone's distribution, the type of receptors it binds to, and other aspects of its function.

release of certain anterior pituitary hormones.

Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

Steroid Hormones

The primary hormones derived from lipids are steroids. Steroid hormones are derived from the lipid cholesterol. For example, the reproductive hormones testosterone and the estrogens—which are produced by the gonads (testes and ovaries)—are steroid hormones. The adrenal glands produce the steroid hormone aldosterone, which is involved in osmoregulation, and cortisol, which plays a role in metabolism.

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel to their target cell bound to a transport protein. This more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. A hormone's half-life is the time required for half the concentration of the hormone to be degraded. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid–derived hormone epinephrine has a half-life of approximately one minute.

Pathways of Hormone Action

The message a hormone sends is received by a **hormone receptor**, a protein located either inside the cell or within the cell membrane. The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell's response. Hormone receptors recognize molecules with specific shapes and side groups, and respond only to those hormones that are recognized. The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses. Thus, the response triggered by a hormone depends not only on the hormone, but also on the target cell.

Once the target cell receives the hormone signal, it can respond in a variety of ways. The response may include the stimulation of protein synthesis, activation or deactivation of enzymes, alteration in the permeability of the cell membrane, altered rates of mitosis and cell growth, and stimulation of the secretion of products. Moreover, a single hormone may be capable of inducing different responses in a given cell.

Pathways Involving Intracellular Hormone Receptors

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor (Figure 17.4). Thyroid hormones, cross the cell membrane by a specific carrier-mediated mechanism that is energy and Na^+ dependent.

The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to a particular segment of the cell's DNA. In contrast, thyroid hormones bind to receptors already bound to DNA. For both steroid and thyroid hormones, binding of the hormone-receptor complex with DNA triggers transcription of a target gene to mRNA, which moves to the cytosol and directs protein synthesis by ribosomes.

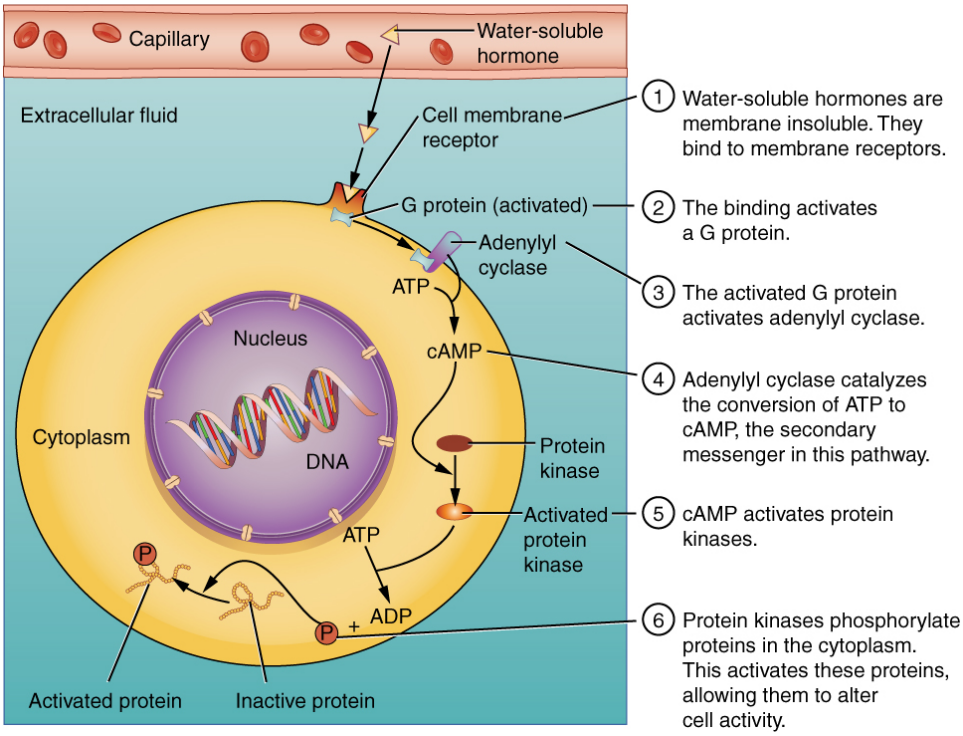


FIGURE 17.5 Binding of Water-Soluble Hormones Water-soluble hormones cannot diffuse through the cell membrane. These hormones must bind to a surface cell-membrane receptor. The receptor then initiates a cell-signaling pathway within the cell involving G proteins, adenylyl cyclase, the secondary messenger cyclic AMP (cAMP), and protein kinases. In the final step, these protein kinases phosphorylate proteins in the cytoplasm. This activates proteins in the cell that carry out the changes specified by the hormone.

The phosphorylation of cellular proteins can trigger a wide variety of effects, from nutrient metabolism to the synthesis of different hormones and other products. The effects vary according to the type of target cell, the G proteins and kinases involved, and the phosphorylation of proteins. Examples of hormones that use cAMP as a second messenger include calcitonin, which is important for bone construction and regulating blood calcium levels; glucagon, which plays a role in blood glucose levels; and thyroid-stimulating hormone, which causes the release of T_3 and T_4 from the thyroid gland.

Overall, the phosphorylation cascade significantly increases the efficiency, speed, and specificity of the hormonal response, as thousands of signaling events can be initiated simultaneously in response to a very low concentration of hormone in the bloodstream. However, the duration of the hormone signal is short, as cAMP is quickly deactivated by the enzyme **phosphodiesterase (PDE)**, which is located in the cytosol. The action of PDE helps to ensure that a target cell's response ceases quickly unless new hormones arrive at the cell membrane.

Importantly, there are also G proteins that decrease the levels of cAMP in the cell in response to hormone binding. For example, when growth hormone–inhibiting hormone (GHIH), also known as somatostatin, binds to its receptors in the pituitary gland, the level of cAMP decreases, thereby inhibiting the secretion of human growth hormone.

Not all water-soluble hormones initiate the cAMP second messenger system. One common alternative system uses calcium ions as a second messenger. In this system, G proteins activate the enzyme phospholipase C (PLC), which functions similarly to adenylyl cyclase. Once activated, PLC cleaves a membrane-bound phospholipid into two molecules: **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)**. Like cAMP, DAG activates protein kinases that initiate a phosphorylation cascade. At the same time, IP_3 causes calcium ions to be released from storage sites within the cytosol, such as from within the smooth endoplasmic reticulum. The calcium ions then act as second messengers in two ways: they can influence enzymatic and other cellular activities directly, or they can bind to calcium-binding proteins, the most common of which is calmodulin. Upon binding calcium, calmodulin is able to modulate protein kinase within the cell. Examples of hormones that use calcium ions as a second messenger system include angiotensin II, which helps regulate blood pressure through vasoconstriction, and growth hormone–releasing hormone (GHRH), which causes the pituitary gland to release growth hormones.

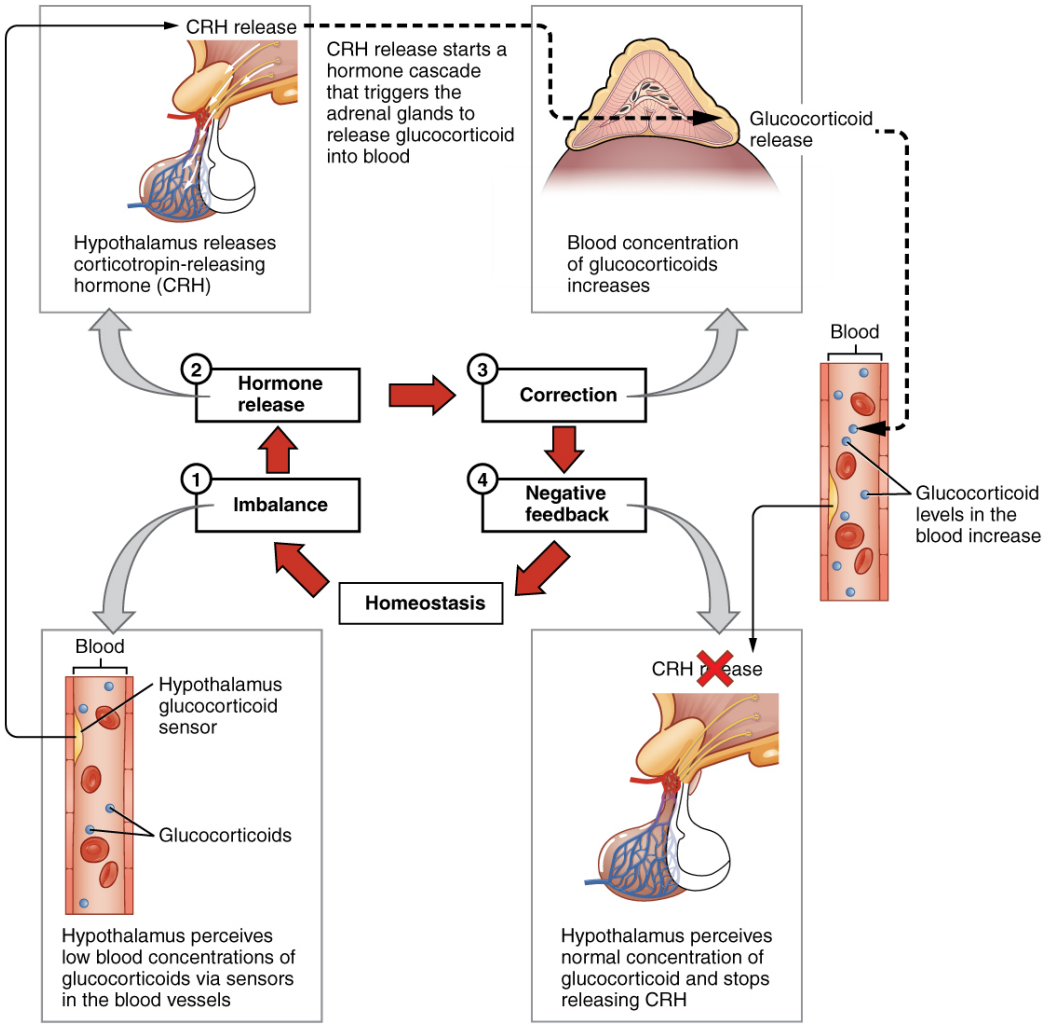


FIGURE 17.6 Negative Feedback Loop The release of adrenal glucocorticoids is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.

Role of Endocrine Gland Stimuli

Reflexes triggered by both chemical and neural stimuli control endocrine activity. These reflexes may be simple, involving only one hormone response, or they may be more complex and involve many hormones, as is the case with the hypothalamic control of various anterior pituitary–controlled hormones.

Humoral stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions, which cause the release or inhibition of a hormone to, in turn, maintain homeostasis. For example, osmoreceptors in the hypothalamus detect changes in blood osmolarity (the concentration of solutes in the blood plasma). If blood osmolarity is too high, meaning that the blood is not dilute enough, osmoreceptors signal the hypothalamus to release ADH. The hormone causes the kidneys to reabsorb more water and reduce the volume of urine produced. This reabsorption causes a reduction of the osmolarity of the blood, diluting the blood to the appropriate level. The regulation of blood glucose is another example. High blood glucose levels cause the release of insulin from the pancreas, which increases glucose uptake by cells and liver storage of glucose as glycogen.

An endocrine gland may also secrete a hormone in response to the presence of another hormone produced by a different endocrine gland. Such hormonal stimuli often involve the hypothalamus, which produces releasing and inhibiting hormones that control the secretion of a variety of pituitary hormones.

In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal glands to secrete norepinephrine and

The **hypothalamus** is a structure of the diencephalon of the brain located anterior and inferior to the thalamus (Figure 17.7). It has both neural and endocrine functions, producing and secreting many hormones. In addition, the hypothalamus is anatomically and functionally related to the **pituitary gland** (or hypophysis), a bean-sized organ suspended from it by a stem called the **infundibulum** (or pituitary stalk). The pituitary gland is cradled within the sellaturcica of the sphenoid bone of the skull. It consists of two lobes that arise from distinct parts of embryonic tissue: the posterior pituitary (neurohypophysis) is neural tissue, whereas the anterior pituitary (also known as the adenohypophysis) is glandular tissue that develops from the primitive digestive tract. The hormones secreted by the posterior and anterior pituitary, and the intermediate zone between the lobes are summarized in Table 17.3.

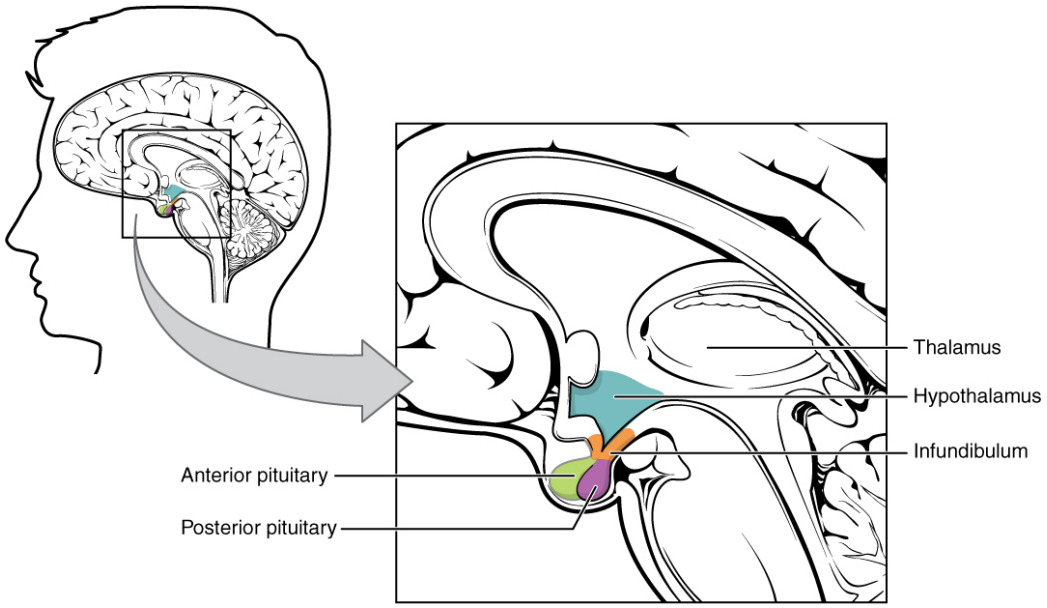


FIGURE 17.7 Hypothalamus–Pituitary Complex The hypothalamus region lies inferior and anterior to the thalamus. It connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland consists of an anterior and posterior lobe, with each lobe secreting different hormones in response to signals from the hypothalamus.

Pituitary Hormones

Pituitary lobe	Associated hormones	Chemical class	Effect
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release from thyroid
Anterior	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Anterior	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production in gonads
Anterior	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads

TABLE 17.3

Oxytocin

When fetal development is complete, the peptide-derived hormone **oxytocin** (tocia- = "childbirth") stimulates uterine contractions and dilation of the cervix. Throughout most of pregnancy, oxytocin hormone receptors are not expressed at high levels in the uterus. Toward the end of pregnancy, the synthesis of oxytocin receptors in the uterus increases, and the smooth muscle cells of the uterus become more sensitive to its effects. Oxytocin is continually released throughout childbirth through a positive feedback mechanism. As noted earlier, oxytocin prompts uterine contractions that push the fetal head toward the cervix. In response, cervical stretching stimulates additional oxytocin to be synthesized by the hypothalamus and released from the pituitary. This increases the intensity and effectiveness of uterine contractions and prompts additional dilation of the cervix. The feedback loop continues until birth.

Although the high blood levels of oxytocin begin to decrease immediately following birth, oxytocin continues to play a role in female and newborn health. First, oxytocin is necessary for the milk ejection reflex (commonly referred to as "let-down") in breastfeeding people. As the newborn begins suckling, sensory receptors in the nipples transmit signals to the hypothalamus. In response, oxytocin is secreted and released into the bloodstream. Within seconds, cells in the milk ducts contract, ejecting milk into the infant's mouth. Secondly, in ball people, oxytocin is thought to contribute to parent–newborn bonding, known as attachment. Oxytocin is also thought to be involved in feelings of love and closeness, as well as in the sexual response.

Antidiuretic Hormone (ADH)

The solute concentration of the blood, or blood osmolarity, may change in response to the consumption of certain foods and fluids, as well as in response to disease, injury, medications, or other factors. Blood osmolarity is constantly monitored by **osmoreceptors**—specialized cells within the hypothalamus that are particularly sensitive to the concentration of sodium ions and other solutes.

In response to high blood osmolarity, which can occur during dehydration or following a very salty meal, the osmoreceptors signal the posterior pituitary to release **antidiuretic hormone (ADH)**. The target cells of ADH are located in the tubular cells of the kidneys. Its effect is to increase epithelial permeability to water, allowing increased water reabsorption. The more water reabsorbed from the filtrate, the greater the amount of water that is returned to the blood and the less that is excreted in the urine. A greater concentration of water results in a reduced concentration of solutes. ADH is also known as vasopressin because, in very high concentrations, it causes constriction of blood vessels, which increases blood pressure by increasing peripheral resistance. The release of ADH is controlled by a negative feedback loop. As blood osmolarity decreases, the hypothalamic osmoreceptors sense the change and prompt a corresponding decrease in the secretion of ADH. As a result, less water is reabsorbed from the urine filtrate.

Interestingly, drugs can affect the secretion of ADH. For example, alcohol consumption inhibits the release of ADH, resulting in increased urine production that can eventually lead to dehydration and a hangover. A disease called diabetes insipidus is characterized by chronic underproduction of ADH that causes chronic dehydration. Because little ADH is produced and secreted, not enough water is reabsorbed by the kidneys. Although patients feel thirsty, and increase their fluid consumption, this doesn't effectively decrease the solute concentration in their blood because ADH levels are not high enough to trigger water reabsorption in the kidneys. Electrolyte imbalances can occur in severe cases of diabetes insipidus.

Anterior Pituitary

The anterior pituitary originates from the digestive tract in the embryo and migrates toward the brain during fetal development. There are three regions: the pars distalis is the most anterior, the pars intermedia is adjacent to the posterior pituitary, and the pars tuberalis is a slender "tube" that wraps the infundibulum.

Recall that the posterior pituitary does not synthesize hormones, but merely stores them. In contrast, the anterior pituitary does manufacture hormones. However, the secretion of hormones from the anterior pituitary is regulated by two classes of hormones. These hormones—secreted by the hypothalamus—are the releasing hormones that stimulate the secretion of hormones from the anterior pituitary and the inhibiting hormones that inhibit secretion.

Hypothalamic hormones are secreted by neurons, but enter the anterior pituitary through blood vessels (Figure 17.9). Within the infundibulum is a bridge of capillaries that connects the hypothalamus to the anterior pituitary.

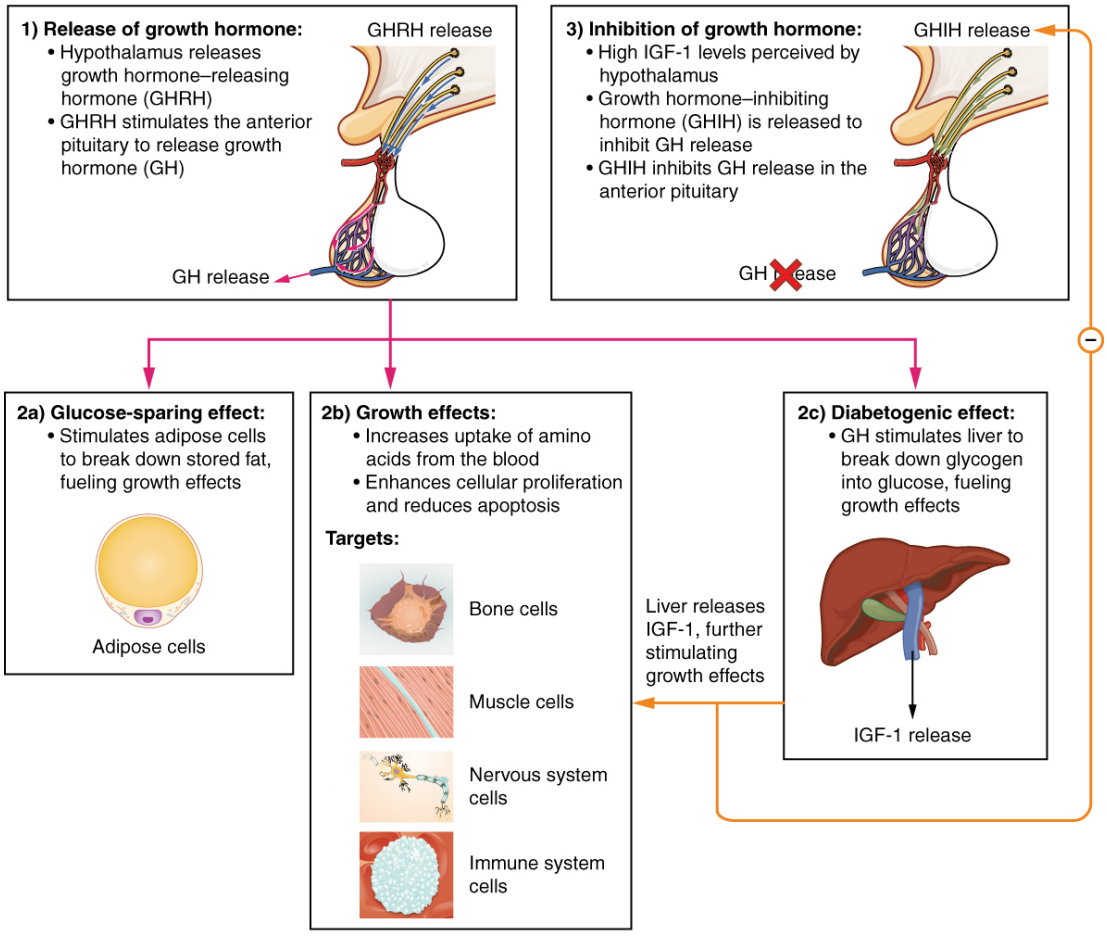


FIGURE 17.10 Hormonal Regulation of Growth Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and indirectly supports the formation of new proteins in muscle cells and bone.

A glucose-sparing effect occurs when GH stimulates lipolysis, or the breakdown of adipose tissue, releasing fatty acids into the blood. As a result, many tissues switch from glucose to fatty acids as their main energy source, which means that less glucose is taken up from the bloodstream.

GH also initiates the diabetogenic effect in which GH stimulates the liver to break down glycogen to glucose, which is then deposited into the blood. The name "diabetogenic" is derived from the similarity in elevated blood glucose levels observed between individuals with untreated diabetes mellitus and individuals experiencing GH excess. Blood glucose levels rise as the result of a combination of glucose-sparing and diabetogenic effects.

GH indirectly mediates growth and protein synthesis by triggering the liver and other tissues to produce a group of proteins called **insulin-like growth factors (IGFs)**. These proteins enhance cellular proliferation and inhibit apoptosis, or programmed cell death. IGFs stimulate cells to increase their uptake of amino acids from the blood for protein synthesis. Skeletal muscle and cartilage cells are particularly sensitive to stimulation from IGFs.

Dysfunction of the endocrine system's control of growth can result in several disorders. For example, **gigantism** is a disorder in children that is caused by the secretion of abnormally large amounts of GH, resulting in excessive growth. A similar condition in adults is **acromegaly**, a disorder that results in the growth of bones in the face, hands, and feet in response to excessive levels of GH in individuals who have stopped growing. Abnormally low levels of GH in children can cause growth impairment—a disorder called **pituitary dwarfism** (also known as growth hormone deficiency).

Thyroid-Stimulating Hormone

The activity of the thyroid gland is regulated by **thyroid-stimulating hormone (TSH)**, also called thyrotropin. TSH is released from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. As

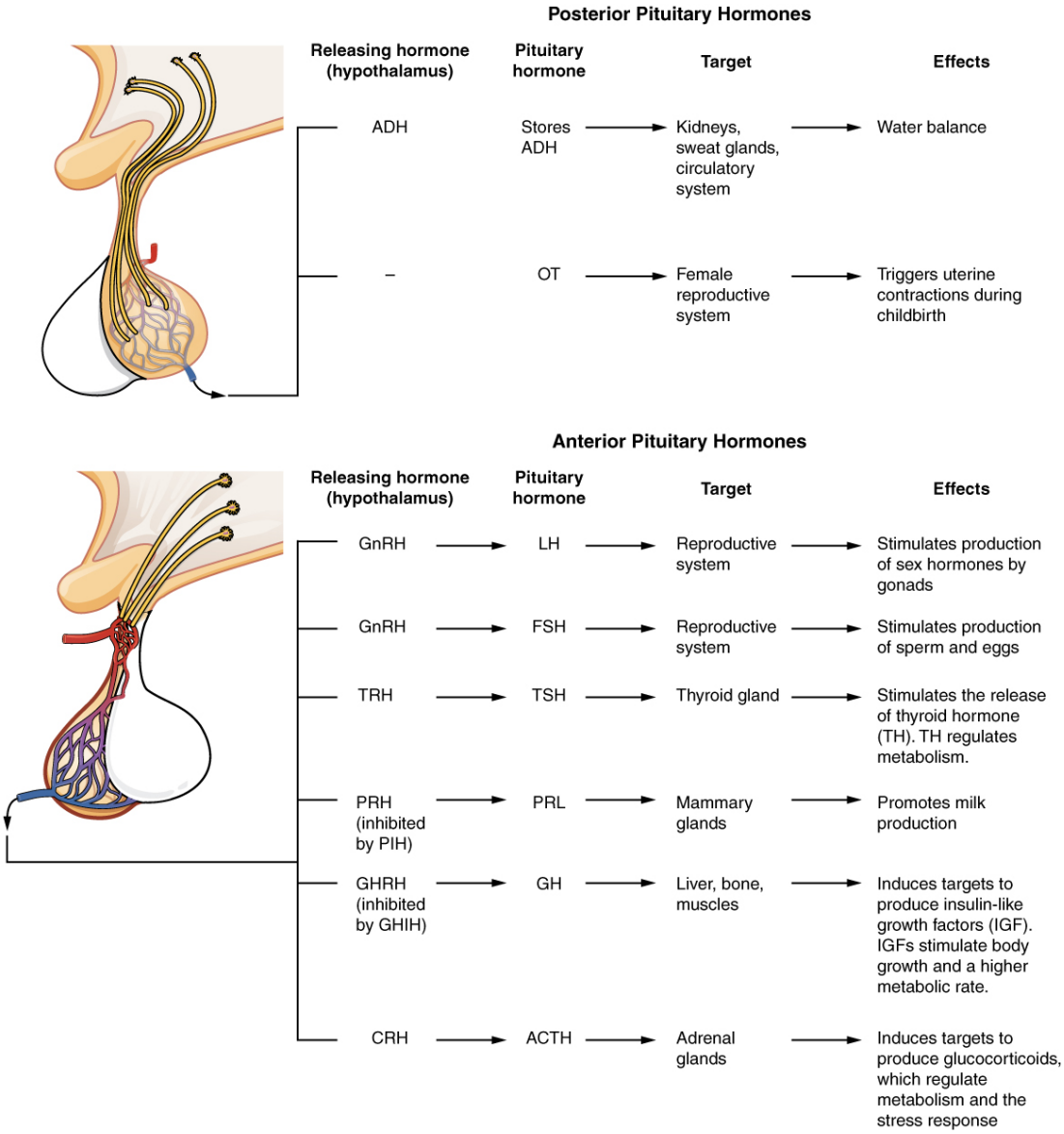


FIGURE 17.11 Major Pituitary Hormones Major pituitary hormones and their target organs.

INTERACTIVE LINK

Visit this link (http://openstax.org/l/roleofhypo) to watch an animation showing the role of the hypothalamus and the pituitary gland. Which hormone is released by the pituitary to stimulate the thyroid gland?

17.4 The Thyroid Gland

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the location and anatomy of the thyroid gland
- Discuss the synthesis of triiodothyronine and thyroxine
- Explain the role of thyroid hormones in the regulation of basal metabolism
- Identify the hormone produced by the parafollicular cells of the thyroid

A butterfly-shaped organ, the **thyroid gland** is located anterior to the trachea, just inferior to the larynx (Figure 17.12). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called

assembly:

1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I^-) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.
2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions ($2\ I^-$) results in iodine (I_2), which passes through the follicle cell membrane into the colloid.
3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is **triiodothyronine** (T_3), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as **thyroxine** (T_4), a thyroid hormone with four iodines.

These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T_3 and T_4, which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T_3 and T_4 remains unbound. This free T_3 and T_4 can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating T_3 and T_4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T_3 and T_4 begin to decline, bound T_3 and T_4 are released from these plasma proteins and readily cross the membrane of target cells. T_3 is more potent than T_4, and many cells convert T_4 to T_3 through the removal of an iodine atom.

Regulation of TH Synthesis

The release of T_3 and T_4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). As shown in Figure 17.13, low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4. The levels of TRH, TSH, T_3, and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH.

Disorders of the...

Endocrine System: Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of T_3 and T_4. But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T_3 and T_4, leading to a variety of severe disorders. When T_3 and T_4 cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a **goiter** (Figure 17.14). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable intellectual disabilies worldwide. **Neonatal hypothyroidism** (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.



FIGURE 17.14 Goiter (credit: "Almazi"/Wikimedia Commons)

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones. Called **hypothyroidism**, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, **hyperthyroidism**—an abnormally elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors, and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

Calcitonin

The thyroid gland also secretes a hormone called **calcitonin** that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium

(Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/parathyroid) to explore the tissue sample in greater detail.

The parathyroid glands produce and secrete PTH, a peptide hormone, in response to low blood calcium levels (Figure 17.16). PTH secretion causes the release of calcium from the bones by stimulating osteoclasts, which secrete enzymes that degrade bone and release calcium into the interstitial fluid. PTH also inhibits osteoblasts, the cells involved in bone deposition, thereby sparing blood calcium. PTH causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate. In addition, PTH initiates the production of the steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D), which is the active form of vitamin D_3, in the kidneys. Calcitriol then stimulates increased absorption of dietary calcium by the intestines. A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting further release of PTH.

gland. As discussed earlier, calcitonin inhibits the activity of osteoclasts, reduces the absorption of dietary calcium in the intestine, and signals the kidneys to reabsorb less calcium, resulting in larger amounts of calcium excreted in the urine.

17.6 The Adrenal Glands

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the location and structure of the adrenal glands
- Identify the hormones produced by the adrenal cortex and adrenal medulla, and summarize their target cells and effects

The **adrenal glands** are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule (Figure 17.17). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.

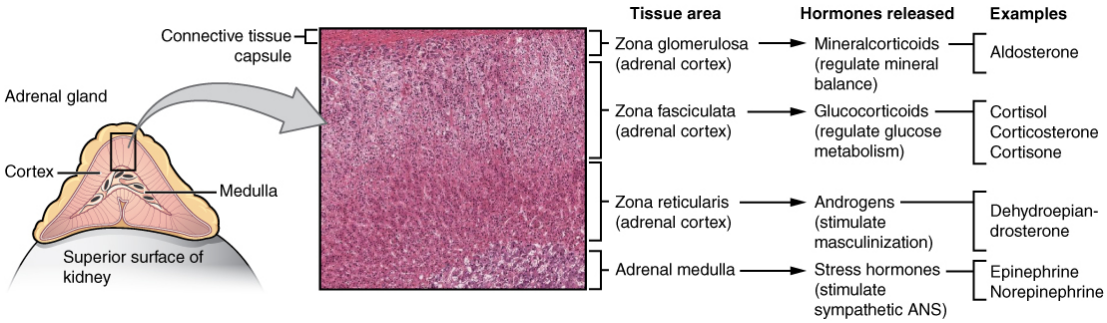


FIGURE 17.17 Adrenal Glands Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. LM × 204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/adrenal) to explore the tissue sample in greater detail.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the **zona glomerulosa**, the **zona fasciculata**, and the **zona reticularis**. Each region secretes its own set of hormones.

The **adrenal cortex**, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The **adrenal medulla** is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the

pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the temporal lobe of the cerebral cortices and important in memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy rashes. These drugs reflect another role of cortisol—the downregulation of the immune system, which inhibits the inflammatory response.

Hormones of the Zona Reticularis

The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult females, they may contribute to the sex drive, but their function in adult males is not well understood. In post-menopausal people, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

Adrenal Medulla

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called **chromaffin** cells, which are large and irregularly shaped, and produce the neurotransmitters **epinephrine** (also called adrenaline) and **norepinephrine** (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways, raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision. The major hormones of the adrenal glands are summarized in Table 17.5.

Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag. Some air travelers take melatonin supplements to induce sleep.

17.8 Gonadal and Placental Hormones

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the most important hormones produced by the testes and ovaries
- Name the hormones produced by the placenta and state their functions

This section briefly discusses the hormonal role of the gonads—the testes and ovaries—which produce the sex cells (sperm and ova) and secrete the gonadal hormones. The roles of the gonadotropins released from the anterior pituitary (FSH and LH) were discussed earlier.

The primary hormone produced by the testes is **testosterone**, a steroid hormone important in the development of the testicular reproductive system, the maturation of sperm cells, and the development of secondary sex characteristics such as a deepened voice, body hair, and increased muscle mass. Interestingly, testosterone is also produced in the ovaries, but at a much reduced level. In addition, the testes produce the peptide hormone **inhibin**, which inhibits the secretion of FSH from the anterior pituitary gland. FSH stimulates spermatogenesis.

The primary hormones produced by the ovaries are **estrogens**, which include estradiol, estriol, and estrone. Estrogens play an important role in a larger number of physiological processes, including the development of the ovarian reproductive system, regulation of the menstrual cycle, the development of secondary sex characteristics such as increased adipose tissue and the development of breast tissue, and the maintenance of pregnancy. Another significant ovarian hormone is **progesterone**, which contributes to regulation of the menstrual cycle and is important in preparing the body for pregnancy as well as maintaining pregnancy. In addition, the granulosa cells of the ovarian follicles produce inhibin, which inhibits the secretion of FSH.During the initial stages of pregnancy, an organ called the placenta develops within the uterus. The placenta supplies oxygen and nutrients to the fetus, excretes waste products, and produces and secretes estrogens and progesterone. The placenta produces human chorionic gonadotropin (hCG) as well. The hCG hormone promotes progesterone synthesis and reduces the mother's immune function to protect the fetus from immune rejection. It also secretes human placental lactogen (hPL), which plays a role in preparing the breasts for lactation, and relaxin, which is thought to help soften and widen the pubic symphysis in preparation for childbirth. The hormones controlling reproduction are summarized in Table 17.6.

Reproductive Hormones

Gonad	Associated hormones	Chemical class	Effect
Testes	Testosterone	Steroid	Stimulates development of secondary sex characteristics and sperm production
Testes	Inhibin	Protein	Inhibits FSH release from pituitary
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of secondary sex characteristics and prepare the body for childbirth
Placenta	Human chorionic gonadotropin	Protein	Promotes progesterone synthesis during pregnancy and inhibits immune response against fetus

TABLE 17.6

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Receptors located in the pancreas sense blood glucose levels, and subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels.

Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting or during prolonged labor or exercise (Figure 17.19). In response, the alpha cells of the pancreas secrete the hormone **glucagon**, which has several effects:

- It stimulates the liver to convert its stores of glycogen back into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids from the blood and convert them into glucose. This response is known as gluconeogenesis.
- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.

to take glucose from the bloodstream, skeletal muscle cells and adipose cells are the primary targets of insulin.

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for insulin production and secretion by the beta cells of the pancreas. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence of insulin, these transport proteins are normally recycled slowly between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior.

INTERACTIVE LINK

Visit this link (http://openstax.org/l/pancreas1) to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis. The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, further insulin release is inhibited. The pancreatic hormones are summarized in Table 17.7.

Hormones of the Pancreas

Associated hormones	Chemical class	Effect
Insulin (beta cells)	Protein	Reduces blood glucose levels
Glucagon (alpha cells)	Protein	Increases blood glucose levels
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release
Pancreatic polypeptide (PP cells)	Protein	Role in appetite

TABLE 17.7

Disorders of the...

Endocrine System: Diabetes Mellitus

Dysfunction of insulin production and secretion, as well as the target cells' responsiveness to insulin, can lead to a condition called **diabetes mellitus**. An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.

peptide (ANP). ANP signals the kidneys to reduce sodium reabsorption, thereby decreasing the amount of water reabsorbed from the urine filtrate and reducing blood volume. Other actions of ANP include the inhibition of renin secretion, thus inhibition of the renin-angiotensin-aldosterone system (RAAS) and vasodilation. Therefore, ANP aids in decreasing blood pressure, blood volume, and blood sodium levels.

Gastrointestinal Tract

The endocrine cells of the GI tract are located in the mucosa of the stomach and small intestine. Some of these hormones are secreted in response to eating a meal and aid in digestion. An example of a hormone secreted by the stomach cells is gastrin, a peptide hormone secreted in response to stomach distention that stimulates the release of hydrochloric acid. Secretin is a peptide hormone secreted by the small intestine as acidic chyme (partially digested food and fluid) moves from the stomach. It stimulates the release of bicarbonate from the pancreas, which buffers the acidic chyme, and inhibits the further secretion of hydrochloric acid by the stomach. Cholecystokinin (CCK) is another peptide hormone released from the small intestine. It promotes the secretion of pancreatic enzymes and the release of bile from the gallbladder, both of which facilitate digestion. Other hormones produced by the intestinal cells aid in glucose metabolism, such as by stimulating the pancreatic beta cells to secrete insulin, reducing glucagon secretion from the alpha cells, or enhancing cellular sensitivity to insulin.

Kidneys

The kidneys participate in several complex endocrine pathways and produce certain hormones. A decline in blood flow to the kidneys stimulates them to release the enzyme renin, triggering the renin-angiotensin-aldosterone (RAAS) system, and stimulating the reabsorption of sodium and water. The reabsorption increases blood flow and blood pressure. The kidneys also play a role in regulating blood calcium levels through the production of calcitriol from vitamin D_3, which is released in response to the secretion of parathyroid hormone (PTH). In addition, the kidneys produce the hormone **erythropoietin (EPO)** in response to low oxygen levels. EPO stimulates the production of red blood cells (erythrocytes) in the bone marrow, thereby increasing oxygen delivery to tissues. You may have heard of EPO as a performance-enhancing drug (in a synthetic form).

Skeleton

Although bone has long been recognized as a target for hormones, only recently have researchers recognized that the skeleton itself produces at least two hormones. Fibroblast growth factor 23 (FGF23) is produced by bone cells in response to increased blood levels of vitamin D_3 or phosphate. It triggers the kidneys to inhibit the formation of calcitriol from vitamin D_3 and to increase phosphorus excretion. Osteocalcin, produced by osteoblasts, stimulates the pancreatic beta cells to increase insulin production. It also acts on peripheral tissues to increase their sensitivity to insulin and their utilization of glucose.

Adipose Tissue

Adipose tissue produces and secretes several hormones involved in lipid metabolism and storage. One important example is **leptin**, a protein manufactured by adipose cells that circulates in amounts directly proportional to levels of body fat. Leptin is released in response to food consumption and acts by binding to brain neurons involved in energy intake and expenditure. Binding of leptin produces a feeling of satiety after a meal, thereby reducing appetite. It also appears that the binding of leptin to brain receptors triggers the sympathetic nervous system to regulate bone metabolism, increasing deposition of cortical bone. Adiponectin—another hormone synthesized by adipose cells—appears to reduce cellular insulin resistance and to protect blood vessels from inflammation and atherosclerosis. Its levels are lower in people who are obese, and rise following weight loss.

Skin

The skin functions as an endocrine organ in the production of the inactive form of vitamin D_3, cholecalciferol. When cholesterol present in the epidermis is exposed to ultraviolet radiation, it is converted to cholecalciferol, which then enters the blood. In the liver, cholecalciferol is converted to an intermediate that travels to the kidneys and is further converted to calcitriol, the active form of vitamin D_3. Vitamin D is important in a variety of physiological processes, including intestinal calcium absorption and immune system function. In some studies, low levels of vitamin D have been associated with increased risks of cancer, severe asthma, and multiple sclerosis. Vitamin D deficiency in children causes rickets, and in adults, osteomalacia—both of which are characterized by bone deterioration.

Organ	Major hormones	Effects
Liver	Insulin-like growth factor-1	Stimulates bodily growth
Liver	Angiotensinogen	Raises blood pressure
Liver	Thrombopoietin	Causes increase in platelets
Liver	Hepcidin	Blocks release of iron into body fluids

TABLE 17.8

17.11 Development and Aging of the Endocrine System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the embryonic origins of the endocrine system
- Discuss the effects of aging on the endocrine system

The endocrine system arises from all three embryonic germ layers. The endocrine glands that produce the steroid hormones, such as the gonads and adrenal cortex, arise from the mesoderm. In contrast, endocrine glands that arise from the endoderm and ectoderm produce the amine, peptide, and protein hormones. The pituitary gland arises from two distinct areas of the ectoderm: the anterior pituitary gland arises from the oral ectoderm, whereas the posterior pituitary gland arises from the neural ectoderm at the base of the hypothalamus. The pineal gland also arises from the ectoderm. The two structures of the adrenal glands arise from two different germ layers: the adrenal cortex from the mesoderm and the adrenal medulla from ectoderm neural cells. The endoderm gives rise to the thyroid and parathyroid glands, as well as the pancreas and the thymus.

As the body ages, changes occur that affect the endocrine system, sometimes altering the production, secretion, and catabolism of hormones. For example, the structure of the anterior pituitary gland changes as vascularization decreases and the connective tissue content increases with increasing age. This restructuring affects the gland's hormone production. For example, the amount of human growth hormone that is produced declines with age, resulting in the reduced muscle mass commonly observed in the elderly.

The adrenal glands also undergo changes as the body ages; as fibrous tissue increases, the production of cortisol and aldosterone decreases. Interestingly, the production and secretion of epinephrine and norepinephrine remain normal throughout the aging process.

A well-known example of the aging process affecting an endocrine gland is menopause and the decline of ovarian function. With increasing age, the ovaries decrease in both size and weight and become progressively less sensitive to gonadotropins. This gradually causes a decrease in estrogen and progesterone levels, leading to menopause and the inability to reproduce. Low levels of estrogens and progesterone are also associated with some disease states, such as osteoporosis, atherosclerosis, and hyperlipidemia, or abnormal blood lipid levels.

Testosterone levels also decline with age, a condition called andropause (or viropause); however, this decline is much less dramatic than the decline of estrogens, and much more gradual, rarely affecting sperm production until very old age. Although this means that males maintain their ability to produce offspring for decades longer than females, the quantity, quality, and motility of their sperm is often reduced.

As the body ages, the thyroid gland produces less of the thyroid hormones, causing a gradual decrease in the basal metabolic rate. The lower metabolic rate reduces the production of body heat and increases levels of body fat. Parathyroid hormones, on the other hand, increase with age. This may be because of reduced dietary calcium levels, causing a compensatory increase in parathyroid hormone. However, increased parathyroid hormone levels combined with decreased levels of calcitonin (and estrogens in females) can lead to osteoporosis as PTH stimulates demineralization of bones to increase blood calcium levels. Notice that osteoporosis is common in all elderly people regardless of sex.

Key Terms

acromegaly disorder in adults caused when abnormally high levels of GH trigger growth of bones in the face, hands, and feet

adenylyl cyclase membrane-bound enzyme that converts ATP to cyclic AMP, creating cAMP, as a result of G-protein activation

adrenal cortex outer region of the adrenal glands consisting of multiple layers of epithelial cells and capillary networks that produces mineralocorticoids and glucocorticoids

adrenal glands endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels

adrenal medulla inner layer of the adrenal glands that plays an important role in the stress response by producing epinephrine and norepinephrine

adrenocorticotropic hormone (ACTH) anterior pituitary hormone that stimulates the adrenal cortex to secrete corticosteroid hormones (also called corticotropin)

alarm reaction the short-term stress, or the fight-or-flight response, of stage one of the general adaptation syndrome mediated by the hormones epinephrine and norepinephrine

aldosterone hormone produced and secreted by the adrenal cortex that stimulates sodium and fluid retention and increases blood volume and blood pressure

alpha cell pancreatic islet cell type that produces the hormone glucagon

angiotensin-converting enzyme the enzyme that converts angiotensin I to angiotensin II

antidiuretic hormone (ADH) hypothalamic hormone that is stored by the posterior pituitary and that signals the kidneys to reabsorb water

atrial natriuretic peptide (ANP) peptide hormone produced by the walls of the atria in response to high blood pressure, blood volume, or blood sodium that reduces the reabsorption of sodium and water in the kidneys and promotes vasodilation

autocrine chemical signal that elicits a response in the same cell that secreted it

beta cell pancreatic islet cell type that produces the hormone insulin

calcitonin peptide hormone produced and secreted by the parafollicular cells (C cells) of the thyroid gland that functions to decrease blood calcium levels

chromaffin neuroendocrine cells of the adrenal medulla

colloid viscous fluid in the central cavity of thyroid follicles, containing the glycoprotein thyroglobulin

cortisol glucocorticoid important in gluconeogenesis, the catabolism of glycogen, and downregulation of the immune system

cyclic adenosine monophosphate (cAMP) second messenger that, in response to adenylyl cyclase activation, triggers a phosphorylation cascade

delta cell minor cell type in the pancreas that secretes the hormone somatostatin

diabetes mellitus condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

diacylglycerol (DAG) molecule that, like cAMP, activates protein kinases, thereby initiating a phosphorylation cascade

downregulation decrease in the number of hormone receptors, typically in response to chronically excessive levels of a hormone

endocrine gland tissue or organ that secretes hormones into the blood and lymph without ducts such that they may be transported to organs distant from the site of secretion

endocrine system cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes

epinephrine primary and most potent catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called adrenaline

erythropoietin (EPO) protein hormone secreted in response to low oxygen levels that triggers the bone marrow to produce red blood cells

estrogens class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy

exocrine system cells, tissues, and organs that secrete substances directly to target tissues via glandular ducts

first messenger hormone that binds to a cell membrane hormone receptor and triggers activation of a second messenger system

follicle-stimulating hormone (FSH) anterior pituitary hormone that stimulates the production and maturation of sex cells

G protein protein associated with a cell membrane hormone receptor that initiates the next step in a second messenger system upon activation by hormone–receptor binding

phosphodiesterase (PDE) cytosolic enzyme that deactivates and degrades cAMP

phosphorylation cascade signaling event in which multiple protein kinases phosphorylate the next protein substrate by transferring a phosphate group from ATP to the protein

pineal gland endocrine gland that secretes melatonin, which is important in regulating the sleep-wake cycle

pinealocyte cell of the pineal gland that produces and secretes the hormone melatonin

pituitary dwarfism disorder in children caused when abnormally low levels of GH result in growth retardation

pituitary gland bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

PP cell minor cell type in the pancreas that secretes the hormone pancreatic polypeptide

progesterone predominantly female sex hormone important in regulating the female reproductive cycle and the maintenance of pregnancy

prolactin (PRL) anterior pituitary hormone that promotes development of the mammary glands and the production of breast milk

protein kinase enzyme that initiates a phosphorylation cascade upon activation

second messenger molecule that initiates a signaling cascade in response to hormone binding on a cell membrane receptor and activation of a G protein

stage of exhaustion stage three of the general adaptation syndrome; the body's long-term response to stress mediated by the hormones of the adrenal cortex

stage of resistance stage two of the general adaptation syndrome; the body's continued response to stress after stage one diminishes

testosterone steroid hormone secreted by the testes and important in the maturation of sperm cells, growth and development of the reproductive system, and the development of secondary sex characteristics

thymosins hormones produced and secreted by the thymus that play an important role in the development and differentiation of T cells

thymus organ that is involved in the development and maturation of T-cells and is particularly active during infancy and childhood

thyroid gland large endocrine gland responsible for the synthesis of thyroid hormones

thyroid-stimulating hormone (TSH) anterior pituitary hormone that triggers secretion of thyroid hormones by the thyroid gland (also called thyrotropin)

thyroxine (also, tetraiodothyronine, T_4) amino acid–derived thyroid hormone that is more abundant but less potent than T_3 and often converted to T_3 by target cells

triiodothyronine (also, T_3) amino acid–derived thyroid hormone that is less abundant but more potent than T_4

upregulation increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

zona fasciculata intermediate region of the adrenal cortex that produce hormones called glucocorticoids

zona glomerulosa most superficial region of the adrenal cortex, which produces the hormones collectively referred to as mineralocorticoids

zona reticularis deepest region of the adrenal cortex, which produces the steroid sex hormones called androgens

Chapter Review

17.1 An Overview of the Endocrine System

The endocrine system consists of cells, tissues, and organs that secrete hormones critical to homeostasis. The body coordinates its functions through two major types of communication: neural and endocrine. Neural communication includes both electrical and chemical signaling between neurons and target cells. Endocrine communication involves chemical signaling via the release of hormones into the extracellular fluid. From there, hormones diffuse into the bloodstream and may travel to distant body regions, where they elicit a response in target cells. Endocrine glands are ductless glands that secrete hormones. Many organs of the body with other primary functions—such as the heart, stomach, and kidneys—also have hormone-secreting cells.

17.2 Hormones

Hormones are derived from amino acids or lipids. Amine hormones originate from the amino acids tryptophan or tyrosine. Larger amino acid hormones include peptides and protein hormones. Steroid hormones are derived from cholesterol.

Steroid hormones and thyroid hormone are lipid soluble. All other amino acid–derived hormones are water soluble. Hydrophobic hormones are able to diffuse through the membrane and interact with an intracellular receptor. In contrast, hydrophilic

17.8 Gonadal and Placental Hormones

The reproductive system is regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) produced by the anterior lobe of the pituitary gland in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. FSH stimulates sperm maturation, which is inhibited by the hormone inhibin. The steroid hormone testosterone, a type of androgen, is released in response to LH and is responsible for the maturation and maintenance of the testicular reproductive system, as well as the development of secondary sex characteristics. FSH also promotes egg maturation and LH signals the secretion of the sex hormones, the estrogens and progesterone. Both of these hormones are important in the development and maintenance of the ovarian reproductive system, as well as maintaining pregnancy. The placenta develops during early pregnancy, and secretes several hormones important for maintaining the pregnancy.

17.9 The Endocrine Pancreas

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide. Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose uptake and utilization by target cells, as well as the storage of excess glucose for later use. Dysfunction of the production of insulin or target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

17.10 Organs with Secondary Endocrine Functions

Some organs have a secondary endocrine function. For example, the walls of the atria of the heart produce the hormone atrial natriuretic peptide (ANP), the gastrointestinal tract produces the hormones gastrin, secretin, and cholecystokinin, which aid in digestion, and the kidneys produce erythropoietin (EPO), which stimulates the formation of red blood cells. Even bone, adipose tissue, and the skin have secondary endocrine functions.

17.11 Development and Aging of the Endocrine System

The endocrine system originates from all three germ layers of the embryo, including the endoderm, ectoderm, and mesoderm. In general, different hormone classes arise from distinct germ layers. Aging affects the endocrine glands, potentially affecting hormone production and secretion, and can cause disease. The production of hormones, such as human growth hormone, cortisol, aldosterone, sex hormones, and the thyroid hormones, decreases with age.

Interactive Link Questions

1. Visit this link (http://openstax.org/l/hormonebind) to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?
2. Visit this link (http://openstax.org/l/roleofhypo) to watch an animation showing the role of the hypothalamus and the pituitary gland. Which hormone is released by the pituitary to stimulate the thyroid gland?
3. Visit this link (http://openstax.org/l/adrenalglands) to view an animation describing the location and function of the adrenal glands. Which hormone produced by the adrenal glands is responsible for mobilization of energy stores?
4. Visit this link (http://openstax.org/l/melatonin) to view an animation describing the function of the hormone melatonin. What should you avoid doing in the middle of your sleep cycle that would lower melatonin?
5. Visit this link (http://openstax.org/l/pancreas1) to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

18. Iodide ions cross from the bloodstream into follicle cells via _____.
a. simple diffusion
b. facilitated diffusion
c. active transport
d. osmosis

19. When blood calcium levels are low, PTH stimulates _____.
a. urinary excretion of calcium by the kidneys
b. a reduction in calcium absorption from the intestines
c. the activity of osteoblasts
d. the activity of osteoclasts

20. Which of the following can result from hyperparathyroidism?
a. increased bone deposition
b. fractures
c. convulsions
d. all of the above

21. The adrenal glands are attached superiorly to which organ?
a. thyroid
b. liver
c. kidneys
d. hypothalamus

22. What secretory cell type is found in the adrenal medulla?
a. chromaffin cells
b. neuroglial cells
c. follicle cells
d. oxyphil cells

23. Cushing's disease is a disorder caused by _____.
a. abnormally low levels of cortisol
b. abnormally high levels of cortisol
c. abnormally low levels of aldosterone
d. abnormally high levels of aldosterone

24. Which of the following responses s not part of the fight-or-flight response?
a. pupil dilation
b. increased oxygen supply to the lungs
c. suppressed digestion
d. reduced mental activity

25. What cells secrete melatonin?
a. melanocytes
b. pinealocytes
c. suprachiasmatic nucleus cells
d. retinal cells

26. The production of melatonin is inhibited by _____.
a. declining levels of light
b. exposure to bright light
c. the secretion of serotonin
d. the activity of pinealocytes

27. The gonads produce what class of hormones?
a. amine hormones
b. peptide hormones
c. steroid hormones
d. catecholamines

28. The production of FSH by the anterior pituitary is reduced by which hormone?
a. estrogens
b. progesterone
c. relaxin
d. inhibin

29. The function of the placental hormone human placental lactogen (hPL) is to _____.
a. prepare the breasts for lactation
b. nourish the placenta
c. regulate the menstrual cycle
d. all of the above

30. If an autoimmune disorder targets the alpha cells, production of which hormone would be directly affected?
a. somatostatin
b. pancreatic polypeptide
c. insulin
d. glucagon

31. Which of the following statements about insulin is true?
a. Insulin acts as a transport protein, carrying glucose across the cell membrane.
b. Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.
c. Insulin stimulates the breakdown of stored glycogen into glucose.
d. Insulin stimulates the kidneys to reabsorb glucose into the bloodstream.

32. The walls of the atria produce which hormone?
a. cholecystokinin
b. atrial natriuretic peptide
c. renin
d. calcitriol

extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma (Figure 18.2). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/normallevels) for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in Figure 18.3.

The three major groups of plasma proteins are as follows:

- **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.
- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.
- **Fibrinogen** is the third of the three major groups of plasma proteins. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor's degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate's degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

18.2 Production of the Formed Elements

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root haima- = "blood"; -poiesis = "production").

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Formed Elements from Stem Cells

All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchal system, with some loss of the ability to diversify at each step. The **totipotent stem cell** is the zygote, or fertilized egg. The totipotent (toti- = "all") stem cell gives rise to all cells of the human body. The next level is the **pluripotent stem cell**, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hematopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hematopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hematopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more

delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.

- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.
  - **Colony-stimulating factors (CSFs)** are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.
  - **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Everyday Connection

Blood Doping

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO_2 max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

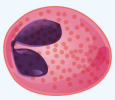
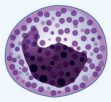
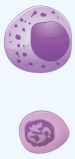
With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/doping) to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone

Formed element	Major subtypes	Numbers present per microliter (μL) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells)		5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	4150 (1800–7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
	Basophils 	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes 	2185 (1500–4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets 		350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

globin, designated alpha 1 and 2, and beta 1 and 2 (Figure 18.7**a**). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron (Fe^{2+}) (Figure 18.7**b**).

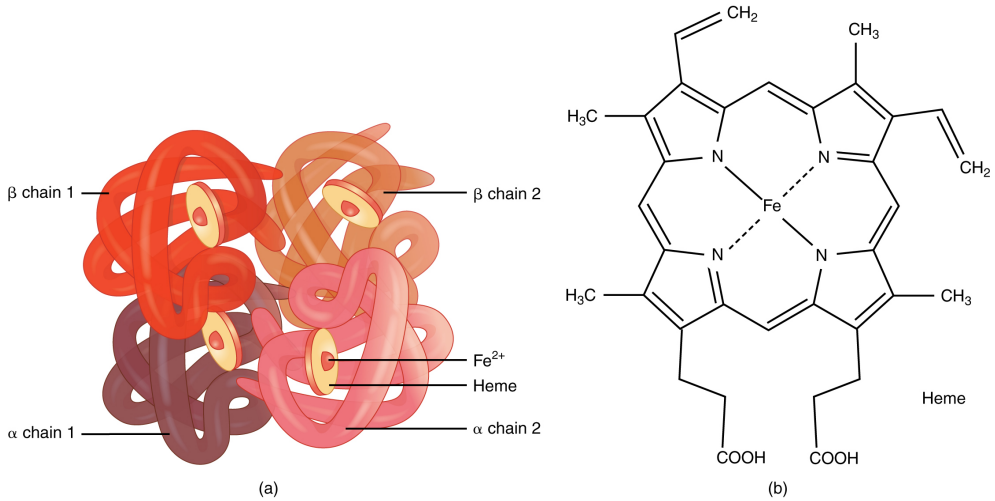


FIGURE 18.7 Hemoglobin (a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see Figure 18.7**b**).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhemoglobin**, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO_2, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect **hypoxemia**, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply P_{O2} or PO2 and is typically recorded in units of millimeters of mercury, mm Hg.

eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with a **bruise**. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with **jaundice**. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized in Figure 18.8.

can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in **sickle cell disease** (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations (Figure 18.9). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.



FIGURE 18.9 Sickle Cells Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet

formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in Figure 18.10, they leave the capillaries—the smallest blood vessels—or other small vessels through a process known as **emigration** (from the Latin for "removal") or **diapedesis** (dia- = "through"; -pedan = "to leap") in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally "movement in response to chemicals"), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical "911" call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.

and basophils (you can view their lineage from myeloid stem cells in Figure 18.4).

- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules (Figure 18.11).

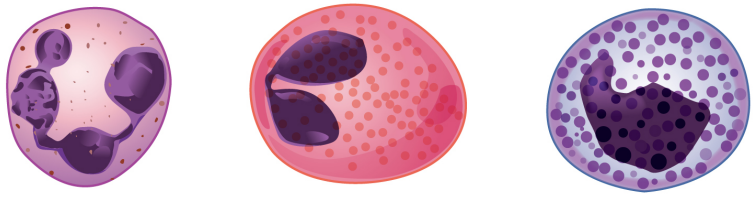


FIGURE 18.11 Granular Leukocytes A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil's granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.

The most common of all the leukocytes, **neutrophils** will normally comprise 50–70 percent of total leukocyte count. They are 10–12 μm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as **polymorphonuclear** (a nucleus with many forms), or simply "polys." Younger and immature neutrophils begin to develop lobes and are known as "bands."

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include **lysozyme**, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and **defensins**, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 μm in diameter. The granules of eosinophils stain best with an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two

capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see Figure 18.4) and are large, typically 50–100 μm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue (Figure 18.12) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These enclosed fragments are platelets. Each megakarocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

Platelets are relatively small, 2–4 μm in diameter, but numerous, with typically 150,000–160,000 per μL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called **thrombocytopenia**, blood may not clot properly, and excessive bleeding may result.

Vascular Spasm

When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In **vascular spasm**, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

Formation of the Platelet Plug

In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing **platelet plug**. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

- adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
- serotonin, which maintains vasoconstriction
- prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals, as discussed next

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches in their hulls until permanent repairs can be made.

Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. Figure 18.14 summarizes the three steps of hemostasis.

Both of these merge into a third pathway, referred to as the common pathway (see Figure 18.14**b**). All three pathways are dependent upon the 12 known clotting factors, including Ca^{2+} and vitamin K (Table 18.1). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

Clotting Factors

Factor number	Name	Type of molecule	Source	Pathway(s)
I	Fibrinogen	Plasma protein	Liver	Common; converted into fibrin
II	Prothrombin	Plasma protein	Liver*	Common; converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic; deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic; deficiency results in hemophilia B
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic; deficiency results in hemophilia C

TABLE 18.1 *Vitamin K required.

Plasma Anticoagulants

An **anticoagulant** is any substance that opposes coagulation. Several circulating plasma anticoagulants play a role in limiting the coagulation process to the region of injury and restoring a normal, clot-free condition of blood. For instance, a cluster of proteins collectively referred to as the protein C system inactivates clotting factors involved in the intrinsic pathway. TFPI (tissue factor pathway inhibitor) inhibits the conversion of the inactive factor VII to the active form in the extrinsic pathway. **Antithrombin** inactivates factor X and opposes the conversion of prothrombin (factor II) to thrombin in the common pathway. And as noted earlier, basophils release **heparin**, a short-acting anticoagulant that also opposes prothrombin. Heparin is also found on the surfaces of cells lining the blood vessels. A pharmaceutical form of heparin is often administered therapeutically, for example, in surgical patients at risk for blood clots.

INTERACTIVE LINK

View these animations (http://openstax.org/l/coagulation) to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Disorders of Clotting

Either an insufficient or an excessive production of platelets can lead to severe disease or death. As discussed earlier, an insufficient number of platelets, called thrombocytopenia, typically results in the inability of blood to form clots. This can lead to excessive bleeding, even from minor wounds.

Another reason for failure of the blood to clot is the inadequate production of functional amounts of one or more clotting factors. This is the case in the genetic disorder **hemophilia**, which is actually a group of related disorders, the most common of which is hemophilia A, accounting for approximately 80 percent of cases. This disorder results in the inability to synthesize sufficient quantities of factor VIII. Hemophilia B is the second most common form, accounting for approximately 20 percent of cases. In this case, there is a deficiency of factor IX. Both of these defects are linked to the X chromosome and are typically passed from a healthy (carrier) female to their male offspring, since males are XY. Females would need to inherit a defective gene from each parent to manifest the disease, since they are XX. Patients with hemophilia bleed from even minor internal and external wounds, and leak blood into joint spaces after exercise and into urine and stool. Hemophilia C is a rare condition that is triggered by an autosomal (not sex) chromosome that renders factor XI nonfunctional. It is not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed. Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = thrombi) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus. Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs, remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an

the load of hemoglobin released can easily overwhelm the kidney's capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

The body must be exposed to a foreign antigen before an antibody can be produced. ABO blood group antigens are found in foods and microbes throughout nature. Thus, the human immune system is exposed to A and B antigens at an early age and antibodies are formed naturally. Individuals with type A blood—without any prior exposure to incompatible blood—have naturally-formed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has naturally-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have naturally-formed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified, only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh^+) and those who lack it are Rh negative (Rh^-). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient's blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A^+) means ABO group A blood with the Rh antigen present, and AB negative (AB^-) means ABO group AB blood without the Rh antigen.

Table 18.2 summarizes the distribution of the ABO and Rh blood types within the United States.

Summary of ABO and Rh Blood Types within the United States

Blood Type	Asian	Black non-Hispanic	Hispanic	North American Indian	White non-Hispanic
A^+	27.3	24.0	28.7	31.3	33.0
A^-	0.5	1.9	2.4	3.8	6.8
B^+	25.0	18.4	9.2	7.0	9.1
B^-	0.4	1.3	0.7	0.9	1.8
AB^+	7.0	4.0	2.3	2.2	3.4
AB^-	0.1	0.3	0.2	0.3	0.7

TABLE 18.2

sensitization. Anti-Rh antibodies begin to circulate in the pregnant person's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh^+ fetus in the uterus. During that subsequent pregnancy, the pregnant person's anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh^- parent, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh^+ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh^- pregnant people during weeks 26–28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh^+ subsequent pregnancy to an Rh^- person is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

Determining ABO Blood Types

Clinicians are able to determine a patient's blood type quickly and easily using commercially prepared antibodies. An unknown blood sample is allocated into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells (Figure 18.16). The blood should also be tested for Rh antibodies.

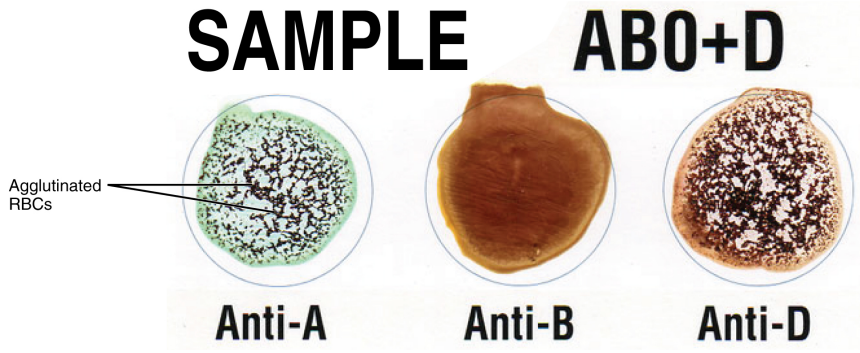


FIGURE 18.16 Cross Matching Blood Types This sample of a commercially produced "bedside" card enables quick typing of both a recipient's and donor's blood before transfusion. The card contains three reaction sites or wells. One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called anti-seras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A^+. For the purpose of transfusion, the donor's and recipient's blood types must match.

ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B^+ recipient should ideally receive blood only from a type B^+ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient's life, there may not be time for cross matching to identify blood type. In these cases, blood from a **universal donor**—an individual with type O^- blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient's blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O^- individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient's own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh^- individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient's blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB^+ is known as the **universal recipient**. This patient can theoretically receive any type of blood, because the patient's own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh^+ patient can receive both Rh^+ and Rh^- blood. However, keep in mind that the donor's blood will contain circulating antibodies, again with possible negative implications. Figure 18.17 summarizes the blood types and compatibilities.

Key Terms

ABO blood group blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination clustering of cells into masses linked by antibodies

agranular leukocytes leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

albumin most abundant plasma protein, accounting for most of the osmotic pressure of plasma

anemia deficiency of red blood cells or hemoglobin

antibodies (also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

anticoagulant substance such as heparin that opposes coagulation

antithrombin anticoagulant that inactivates factor X and opposes the conversion of prothrombin (factor II) into thrombin in the common pathway

B lymphocytes (also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

basophils granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

bilirubin yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

biliverdin green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver

blood liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

bone marrow biopsy diagnostic test of a sample of red bone marrow

bone marrow transplant treatment in which a donor's healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient

bruise localized bleeding under the skin due to damaged blood vessels

buffy coat thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

carbaminohemoglobin compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

clotting factors group of 12 identified substances active in coagulation

coagulation formation of a blood clot; part of the process of hemostasis

colony-stimulating factors (CSFs) glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)

common pathway final coagulation pathway activated either by the intrinsic or the extrinsic pathway, and ending in the formation of a blood clot

cross matching blood test for identification of blood type using antibodies and small samples of blood

cytokines class of proteins that act as autocrine or paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

defensins antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

deoxyhemoglobin molecule of hemoglobin without an oxygen molecule bound to it

diapedesis (also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

embolus thrombus that has broken free from the blood vessel wall and entered the circulation

emigration (also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

eosinophils granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

erythrocyte (also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

erythropoietin (EPO) glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels

extrinsic pathway initial coagulation pathway that begins with tissue damage and results in the activation of the common pathway

ferritin protein-containing storage form of iron found in the bone marrow, liver, and spleen

fibrin insoluble, filamentous protein that forms the structure of a blood clot

fibrinogen plasma protein produced in the liver and involved in blood clotting

fibrinolysis gradual degradation of a blood clot

formed elements cellular components of blood; that is, erythrocytes, leukocytes, and platelets

globin heme-containing globular protein that is a

formed elements and dissolved materials throughout the cardiovascular system

plasmin blood protein active in fibrinolysis

platelet plug accumulation and adhesion of platelets at the site of blood vessel injury

platelets (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

pluripotent stem cell stem cell that derives from totipotent stem cells and is capable of differentiating into many, but not all, cell types

polycythemia elevated level of hemoglobin, whether adaptive or pathological

polymorphonuclear having a lobed nucleus, as seen in some leukocytes

positive chemotaxis process in which a cell is attracted to move in the direction of chemical stimuli

red blood cells (RBCs) (also, erythrocytes) one of the formed elements of blood that transports oxygen

reticulocyte immature erythrocyte that may still contain fragments of organelles

Rh blood group blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

serum blood plasma that does not contain clotting factors

sickle cell disease (also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

T lymphocytes (also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thalassemia inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

thrombin enzyme essential for the final steps in formation of a fibrin clot

thrombocytes platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

thrombopoietin hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)

thrombosis excessive clot formation

thrombus aggregation of fibrin, platelets, and erythrocytes in an intact artery or vein

tissue factor protein thromboplastin, which initiates the extrinsic pathway when released in response to tissue damage

totipotent stem cell embryonic stem cell that is capable of differentiating into any and all cells of the body; enabling the full development of an organism

transferrin plasma protein that binds reversibly to iron and distributes it throughout the body

universal donor individual with type O^- blood

universal recipient individual with type AB^+ blood

vascular spasm initial step in hemostasis, in which the smooth muscle in the walls of the ruptured or damaged blood vessel contracts

white blood cells (WBCs) (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

Chapter Review

18.1 An Overview of Blood

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water. The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

18.2 Production of the Formed Elements

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hematopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin,

Interactive Link Questions

1. Visit this site (http://openstax.org/l/normallevels) for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?
2. Watch this video (http://openstax.org/l/doping) to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?
3. Figure 18.13 Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?
4. View these animations (http://openstax.org/l/coagulation) to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Review Questions

5. Which of the following statements about blood is true?
   a. Blood is about 92 percent water.
   b. Blood is slightly more acidic than water.
   c. Blood is slightly more viscous than water.
   d. Blood is slightly more salty than seawater.
6. Which of the following statements about albumin is true?
   a. It draws water out of the blood vessels and into the body's tissues.
   b. It is the most abundant plasma protein.
   c. It is produced by specialized leukocytes called plasma cells.
   d. All of the above are true.
7. Which of the following plasma proteins is *not* produced by the liver?
   a. fibrinogen
   b. alpha globulin
   c. beta globulin
   d. immunoglobulin
8. Which of the formed elements arise from myeloid stem cells?
   a. B cells
   b. natural killer cells
   c. platelets
   d. all of the above
9. Which of the following statements about erythropoietin is true?
   a. It facilitates the proliferation and differentiation of the erythrocyte lineage.
   b. It is a hormone produced by the thyroid gland.
   c. It is a hemopoietic growth factor that prompts lymphoid stem cells to leave the bone marrow.
   d. Both a and b are true.
10. Interleukins are associated primarily with which of the following?
    a. production of various lymphocytes
    b. immune responses
    c. inflammation
    d. all of the above
11. Which of the following statements about mature, circulating erythrocytes is true?
    a. They have no nucleus.
    b. They are packed with mitochondria.
    c. They survive for an average of 4 days.
    d. All of the above
12. A molecule of hemoglobin _____.
    a. is shaped like a biconcave disk packed almost entirely with iron
    b. contains four glycoprotein units studded with oxygen
    c. consists of four globin proteins, each bound to a molecule of heme
    d. can carry up to 120 molecules of oxygen

Critical Thinking Questions

27. A patient's hematocrit is 42 percent. Approximately what percentage of the patient's blood is plasma?

28. Why would it be incorrect to refer to the formed elements as cells?

29. True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.

30. Myelofibrosis is a disorder in which inflammation and scar tissue formation in the bone marrow impair hemopoiesis. One sign is an enlarged spleen. Why?

31. Would you expect a patient with a form of cancer called acute myelogenous leukemia to experience impaired production of erythrocytes, or impaired production of lymphocytes? Explain your choice.

32. A young person has been experiencing unusually heavy menstrual bleeding for several years. They follow a strict vegan diet (no animal foods). They are is at risk for what disorder, and why?

33. A patient has thalassemia, a genetic disorder characterized by abnormal synthesis of globin proteins and excessive destruction of erythrocytes. This patient is jaundiced and is found to have an excessive level of bilirubin in their blood. Explain the connection.

34. One of the more common adverse effects of cancer chemotherapy is the destruction of leukocytes. Before his next scheduled chemotherapy treatment, a patient undergoes a blood test called an absolute neutrophil count (ANC), which reveals that his neutrophil count is 1900 cells per microliter. Would his healthcare team be likely to proceed with his chemotherapy treatment? Why?

35. A patient was admitted to the burn unit the previous evening suffering from a severe burn involving their left upper extremity and shoulder. A blood test reveals that they are experiencing leukocytosis. Why is this an expected finding?

36. A lab technician collects a blood sample in a glass tube. After about an hour, she harvests serum to continue her blood analysis. Explain what has happened during the hour that the sample was in the glass tube.

37. Explain why administration of a thrombolytic agent is a first intervention for someone who has suffered a thrombotic stroke.

38. Following a motor vehicle accident, a patient is rushed to the emergency department with multiple traumatic injuries, causing severe bleeding. The patient's condition is critical, and there is no time for determining their blood type. What type of blood is transfused, and why?

39. In preparation for a scheduled surgery, a patient visits the hospital lab for a blood draw. The technician collects a blood sample and performs a test to determine its type. She places a sample of the patient's blood in two wells. To the first well she adds anti-A antibody. To the second she adds anti-B antibody. Both samples visibly agglutinate. Has the technician made an error, or is this a normal response? If normal, what blood type does this indicate?

19.1 Heart Anatomy

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity
- Describe the internal and external anatomy of the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Compare systemic circulation to pulmonary circulation
- Identify the veins and arteries of the coronary circulation system
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart

The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. Figure 19.2 shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in Figure 19.2. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.

mannequin.

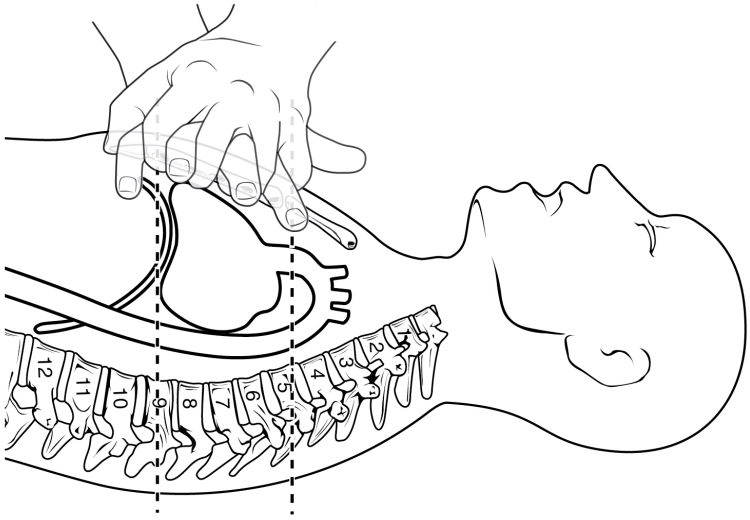


FIGURE 19.3 CPR Technique If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

INTERACTIVE LINK

Visit the American Heart Association website (http://openstax.org/l/AHA) to help locate a course near your home in the United States. There are also many other national and regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex (see Figure 19.2). A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **systemic circuit** transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

Membranes, Surface Features, and Layers

Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the **pericardium** or **pericardial sac**. It also surrounds the "roots" of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as "around the heart," consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a **mesothelium**, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. Figure 19.5 illustrates the pericardial membrane and the layers of the heart.

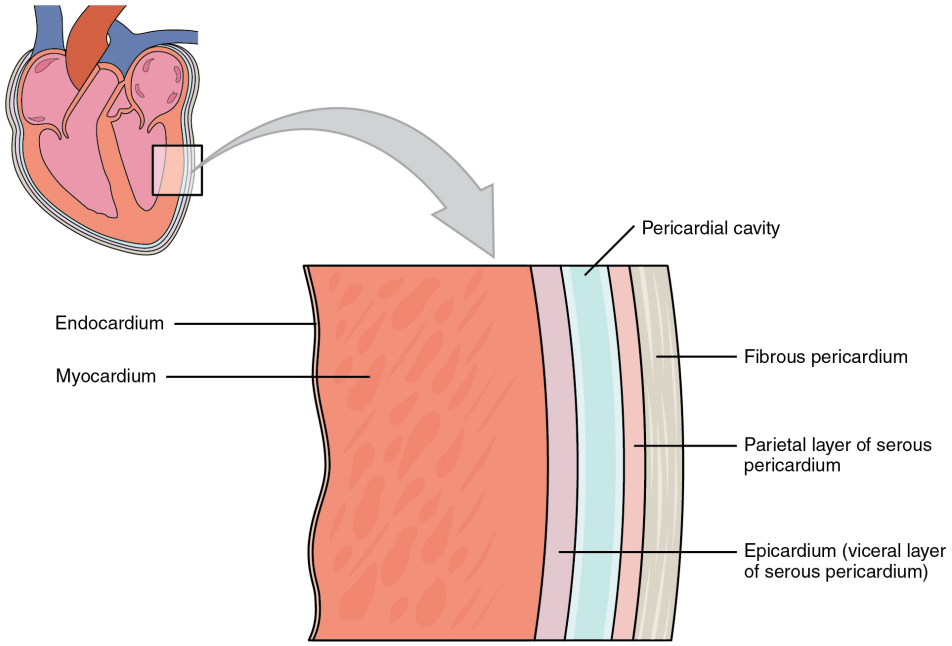


FIGURE 19.5 Pericardial Membranes and Layers of the Heart Wall The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

Disorders of the...

Heart: Cardiac Tamponade

If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates

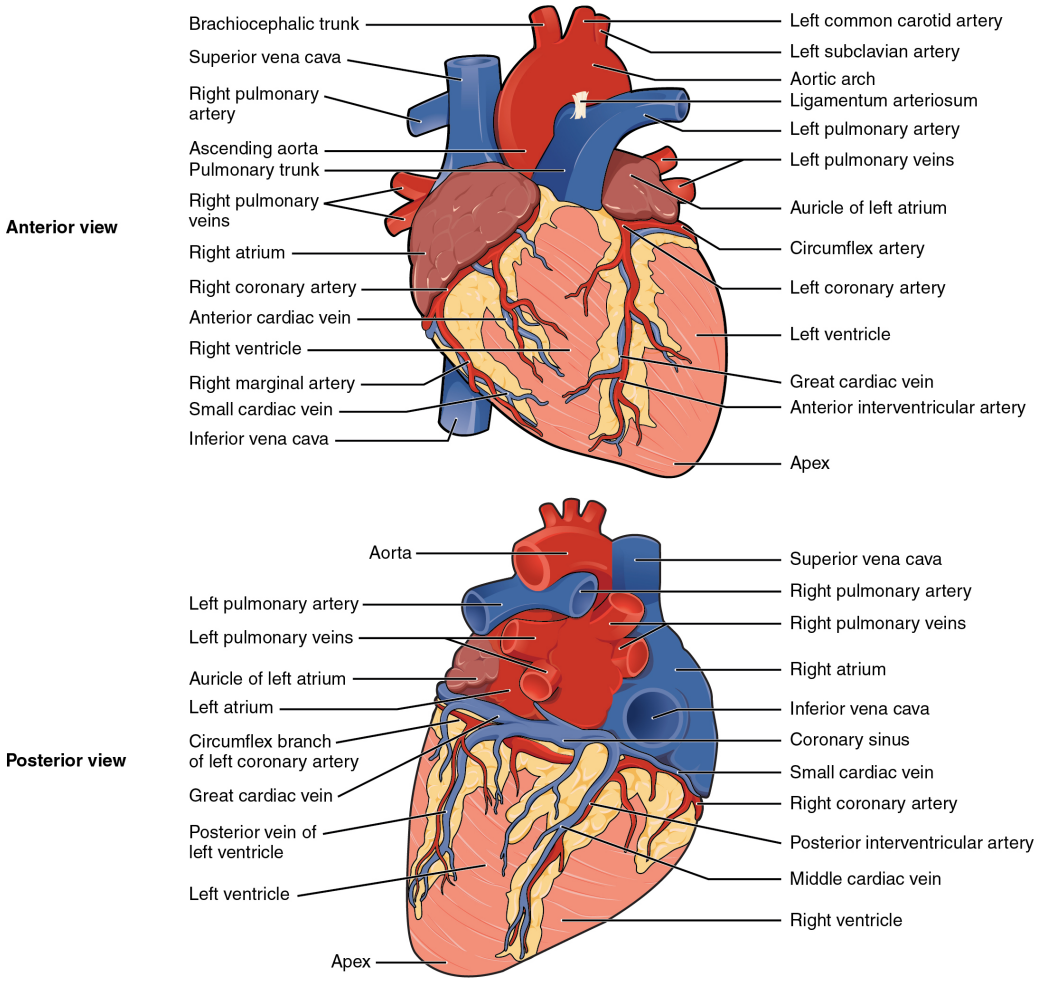


FIGURE 19.6 External Anatomy of the Heart Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see Figure 19.5). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. Figure 19.7 illustrates the arrangement of muscle cells.

it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

The word septum is derived from the Latin for "something that encloses;" in this case, a **septum** (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the **interatrial septum**. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the **fossa ovalis**, a remnant of an opening in the fetal heart known as the **foramen ovale**. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the **septum primum** that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum**. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a **valve**, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular valves**. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as **semilunar valves**. The interventricular septum is visible in Figure 19.9. In this figure, the atrioventricular septum has been removed to better show the bicuspid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton**, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term "tetralogy" is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a "blue baby." Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in Figure 19.10.

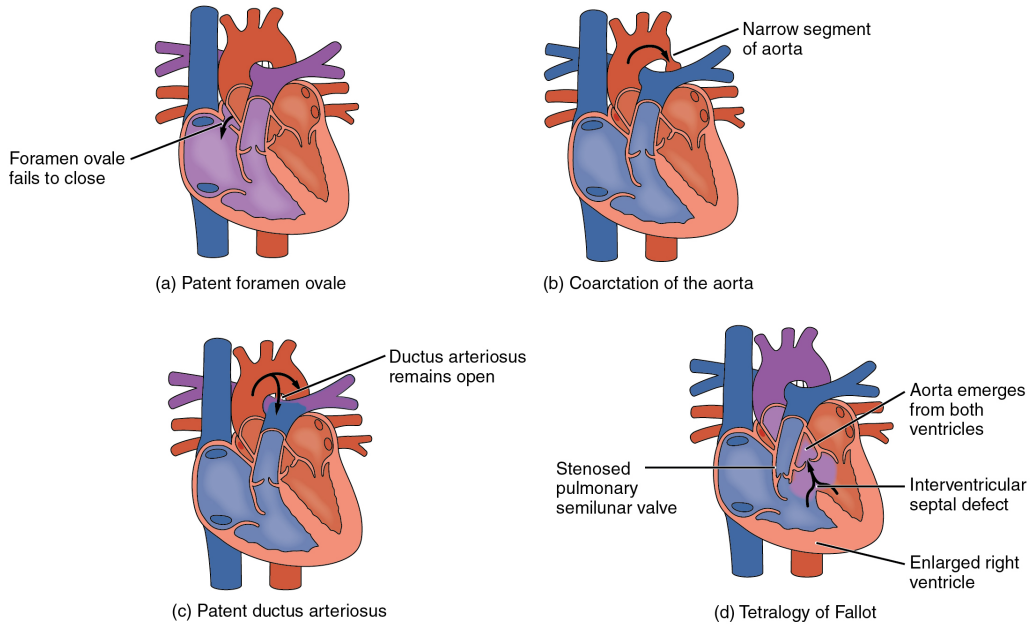


FIGURE 19.10 Congenital Heart Defects (a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The

band (see Figure 19.9) reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right (see Figure 19.8). Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane (Figure 19.12). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.

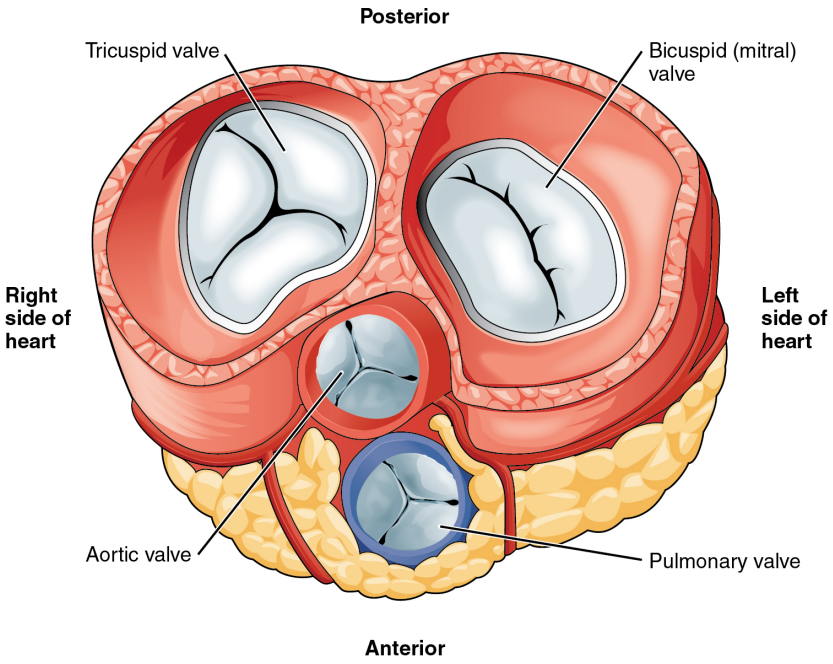


FIGURE 19.12 Heart Valves With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

prevents blood from being forced back into the atria. This stage can be seen from a frontal view in Figure 19.14**b**.

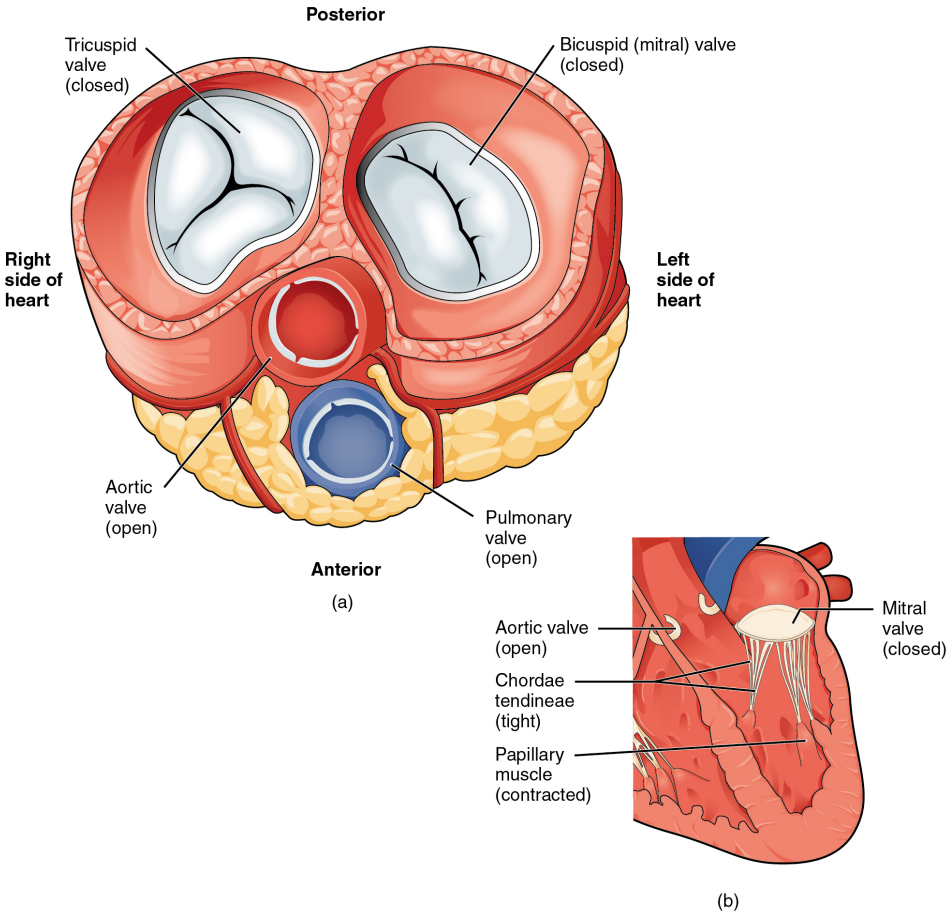


FIGURE 19.14 Blood Flow from the Left Ventricle into the Great Vessels (a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight (see Figure 19.13**b**). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see Figure 19.14**b**), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/heartvalve) to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/cardiologist) to learn more about cardiologists.

CAREER CONNECTION

Cardiovascular Technologist/Technician

Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of $49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.

There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

INTERACTIVE LINK

Visit this site (http://openstax.org/l/cardiotech) for more information on cardiovascular technologists/technicians.

Coronary Circulation

You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger **anterior interventricular artery**, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An **anastomosis** is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the

exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel.

In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient's ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells.

Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as "bad" cholesterol), low levels of high-density lipoprotein (HDL, or "good" cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries (see Figure 19.15). The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the anterior interventricular artery and drains the areas supplied by this vessel. It receives several major branches, including the posterior cardiac vein, the middle cardiac vein, and the small cardiac vein. The **posterior cardiac vein** parallels and drains the areas supplied by the marginal artery branch of the circumflex artery. The **middle cardiac vein** parallels and drains the areas supplied by the posterior interventricular artery. The **small cardiac vein** parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

19.2 Cardiac Muscle and Electrical Activity

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure of cardiac muscle
- Identify and describe the components of the conducting system that distributes electrical impulses through the heart
- Compare the effect of ion movement on membrane potential of cardiac conductive and contractile cells
- Relate characteristics of an electrocardiogram to events in the cardiac cycle
- Identify blocks that can interrupt the cardiac cycle

Recall that cardiac muscle shares a few characteristics with both skeletal muscle and smooth muscle, but it has some unique properties of its own. Not the least of these exceptional properties is its ability to initiate an electrical potential at a fixed rate that spreads rapidly from cell to cell to trigger the contractile mechanism. This property is known as **autorhythmicity**. Neither smooth nor skeletal muscle can do this. Even though cardiac muscle has autorhythmicity, heart rate is modulated by the endocrine and nervous systems.

There are two major types of cardiac muscle cells: myocardial contractile cells and myocardial conducting cells. The **myocardial contractile cells** constitute the bulk (99 percent) of the cells in the atria and ventricles. Contractile cells conduct impulses and are responsible for contractions that pump blood through the body. The **myocardial conducting cells** (1 percent of the cells) form the conduction system of the heart. Except for Purkinje cells, they are generally much smaller than the contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons, although they are specialized muscle cells. Myocardial conduction cells initiate and propagate the action potential (the electrical impulse) that travels throughout the heart and triggers the contractions that propel the blood.

Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell (Figure 19.17**a**). These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle. In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells.

Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle (Figure 19.17**b**). The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions between the cells and help to synchronize the contraction (Figure 19.17**c**). Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.

will be greatly enhanced. To date, myocardial cells produced within the patient (*in situ*) by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes (*in vitro*) do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

Conduction System of the Heart

If embryonic heart cells are separated into a Petri dish and kept alive, each is capable of generating its own electrical impulse followed by contraction. When two independently beating embryonic cardiac muscle cells are placed together, the cell with the higher inherent rate sets the pace, and the impulse spreads from the faster to the slower cell to trigger a contraction. As more cells are joined together, the fastest cell continues to assume control of the rate. A fully developed adult heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, as part of the cardiac conduction system. The components of the cardiac conduction system include the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches, and the Purkinje cells (Figure 19.18).

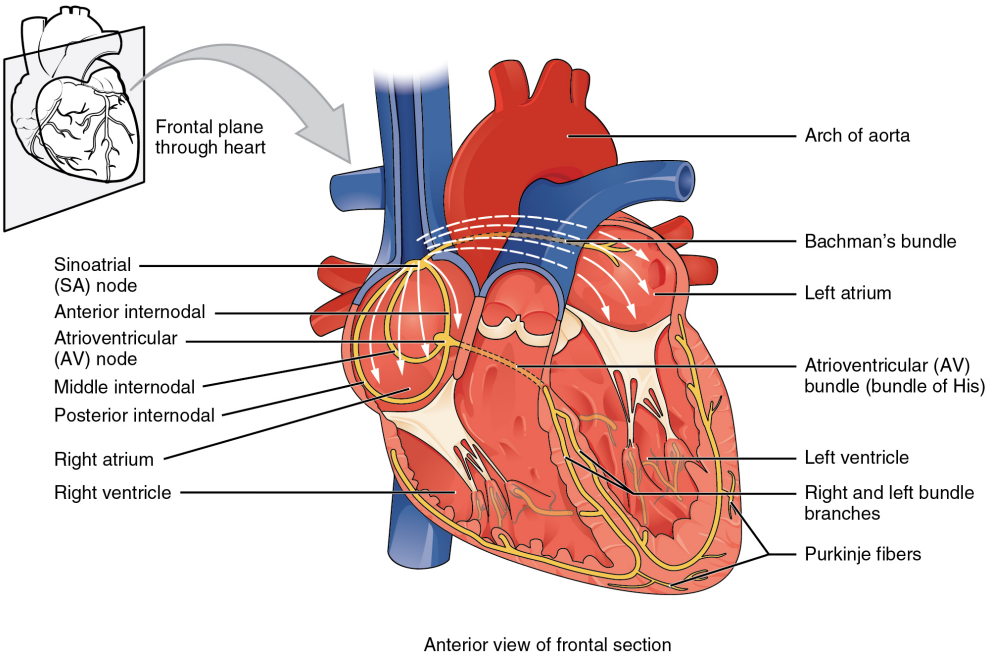


FIGURE 19.18 Conduction System of the Heart Specialized conducting components of the heart include the sinoatrial node, the internodal pathways, the atrioventricular node, the atrioventricular bundle, the right and left bundle branches, and the Purkinje fibers.

Sinoatrial (SA) Node

Normal cardiac rhythm is established by the **sinoatrial (SA) node**, a specialized clump of myocardial conducting cells located in the superior and posterior walls of the right atrium in close proximity to the orifice of the superior vena cava. The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart. It initiates the **sinus rhythm**, or normal electrical pattern followed by contraction of the heart.

This impulse spreads from its initiation in the SA node throughout the atria through specialized **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular node. The internodal pathways consist of three bands (anterior, middle, and posterior) that lead directly from the SA node to the next node in the conduction system, the atrioventricular node (see Figure 19.18). The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called **Bachmann's bundle** or the **interatrial band** that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. Figure 19.19 illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to

considerably larger than the right. Portions of the right bundle branch are found in the moderator band and supply the right papillary muscles. Because of this connection, each papillary muscle receives the impulse at approximately the same time, so they begin to contract simultaneously just prior to the remainder of the myocardial contractile cells of the ventricles. This is believed to allow tension to develop on the chordae tendineae prior to right ventricular contraction. There is no corresponding moderator band on the left. Both bundle branches descend and reach the apex of the heart where they connect with the Purkinje fibers (see Figure 19.19, step 4). This passage takes approximately 25 ms.

The **Purkinje fibers** are additional myocardial conductive fibers that spread the impulse to the myocardial contractile cells in the ventricles. They extend throughout the myocardium from the apex of the heart toward the atrioventricular septum and the base of the heart. The Purkinje fibers have a fast inherent conduction rate, and the electrical impulse reaches all of the ventricular muscle cells in about 75 ms (see Figure 19.19, step 5). Since the electrical stimulus begins at the apex, the contraction also begins at the apex and travels toward the base of the heart, similar to squeezing a tube of toothpaste from the bottom. This allows the blood to be pumped out of the ventricles and into the aorta and pulmonary trunk. The total time elapsed from the initiation of the impulse in the SA node until depolarization of the ventricles is approximately 225 ms.

Membrane Potentials and Ion Movement in Cardiac Conductive Cells

Action potentials are considerably different between cardiac conductive cells and cardiac contractive cells. While Na^+ and K^+ play essential roles, Ca^{2+} is also critical for both types of cells. Unlike skeletal muscles and neurons, cardiac conductive cells do not have a stable resting potential. Conductive cells contain a series of sodium ion channels that allow a normal and slow influx of sodium ions that causes the membrane potential to rise slowly from an initial value of −60 mV up to about −40 mV. The resulting movement of sodium ions creates **spontaneous depolarization** (or **prepotential depolarization**). At this point, calcium ion channels open and Ca^{2+} enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately +15 mV. At this point, the calcium ion channels close and K^+ channels open, allowing outflux of K^+ and resulting in repolarization. When the membrane potential reaches approximately −60 mV, the K^+ channels close and Na^+ channels open, and the prepotential phase begins again. This phenomenon explains the autorhythmicity properties of cardiac muscle (Figure 19.20).

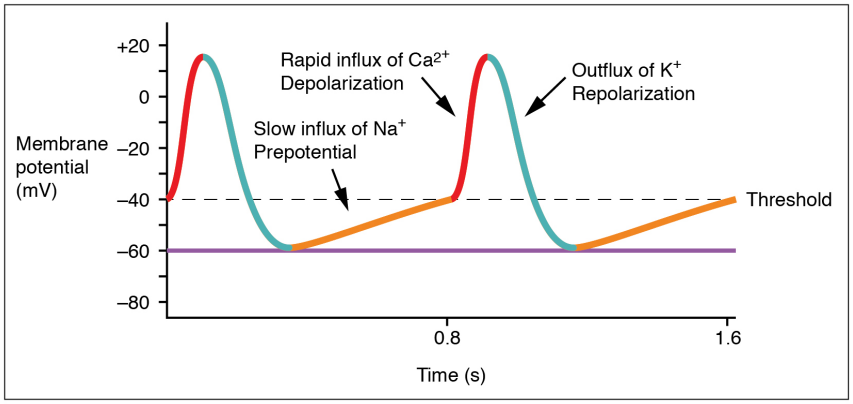


FIGURE 19.20 Action Potential at the SA Node The prepotential is due to a slow influx of sodium ions until the threshold is reached followed by a rapid depolarization and repolarization. The prepotential accounts for the membrane reaching threshold and initiates the spontaneous depolarization and contraction of the cell. Note the lack of a resting potential.

Membrane Potentials and Ion Movement in Cardiac Contractile Cells

There is a distinctly different electrical pattern involving the contractile cells. In this case, there is a rapid depolarization, followed by a plateau phase and then repolarization. This phenomenon accounts for the long refractory periods required for the cardiac muscle cells to pump blood effectively before they are capable of firing for a second time. These cardiac myocytes normally do not initiate their own electrical potential but rather wait for an impulse to reach them.

Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately −80 mV for cells in the atria and −90 mV for cells in the ventricles. Despite this initial difference, the other components of their action potentials are virtually identical. In both cases, when stimulated by an action potential, voltage-gated

the active sites on actin that provide the power stroke of contraction. This mechanism is virtually identical to that of skeletal muscle. Approximately 20 percent of the calcium required for contraction is supplied by the influx of Ca^{2+} during the plateau phase. The remaining Ca^{2+} for contraction is released from storage in the sarcoplasmic reticulum.

Comparative Rates of Conduction System Firing

The pattern of prepotential or spontaneous depolarization, followed by rapid depolarization and repolarization just described, are seen in the SA node and a few other conductive cells in the heart. Since the SA node is the pacemaker, it reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells. The SA node, without nervous or endocrine control, would initiate a heart impulse approximately 80–100 times per minute. Although each component of the conduction system is capable of generating its own impulse, the rate progressively slows as you proceed from the SA node to the Purkinje fibers. Without the SA node, the AV node would generate a heart rate of 40–60 beats per minute. If the AV node were blocked, the atrioventricular bundle would fire at a rate of approximately 30–40 impulses per minute. The bundle branches would have an inherent rate of 20–30 impulses per minute, and the Purkinje fibers would fire at 15–20 impulses per minute. While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute (the lowest recorded figure is 28 beats per minute for Miguel Indurain, a cyclist), for most individuals, rates lower than 50 beats per minute would indicate a condition called bradycardia. Depending upon the specific individual, as rates fall much below this level, the heart would be unable to maintain adequate flow of blood to vital tissues, initially resulting in decreasing loss of function across the systems, unconsciousness, and ultimately death.

Electrocardiogram

By careful placement of surface electrodes on the body, it is possible to record the complex, compound electrical signal of the heart. This tracing of the electrical signal is the **electrocardiogram (ECG)**, also commonly abbreviated EKG (K coming kardiology, from the German term for cardiology). Careful analysis of the ECG reveals a detailed picture of both normal and abnormal heart function, and is an indispensable clinical diagnostic tool. The standard electrocardiograph (the instrument that generates an ECG) uses 3, 5, or 12 leads. The greater the number of leads an electrocardiograph uses, the more information the ECG provides. The term “lead” may be used to refer to the cable from the electrode to the electrical recorder, but it typically describes the voltage difference between two of the electrodes. The 12-lead electrocardiograph uses 10 electrodes placed in standard locations on the patient’s skin (Figure 19.22). In continuous ambulatory electrocardiographs, the patient wears a small, portable, battery-operated device known as a Holter monitor, or simply a Holter, that continuously monitors heart electrical activity, typically for a period of 24 hours during the patient’s normal routine.

would be visible in the PR interval. Figure 19.24 correlates events of heart contraction to the corresponding segments and intervals of an ECG.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/ECG) for a more detailed analysis of ECGs.

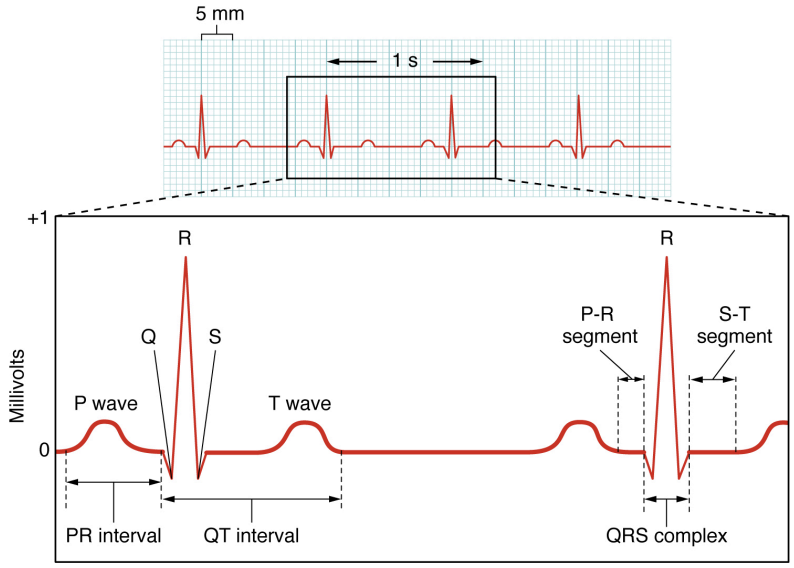


FIGURE 19.23 Electrocardiogram A normal tracing shows the P wave, QRS complex, and T wave. Also indicated are the PR, QT, QRS, and ST intervals, plus the P-R and S-T segments.

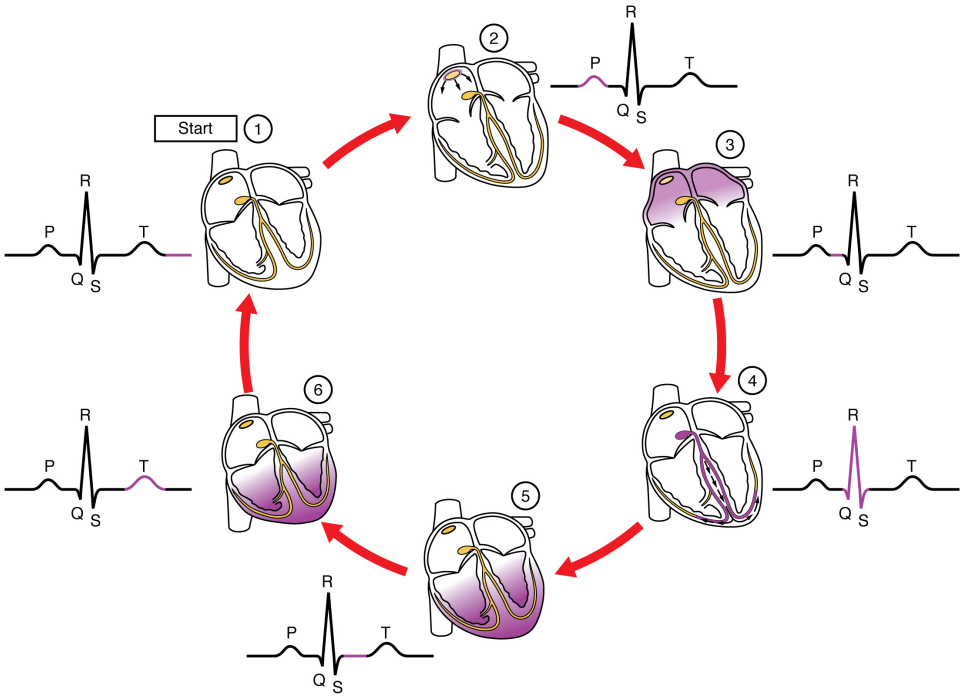


FIGURE 19.24 ECG Tracing Correlated to the Cardiac Cycle This diagram correlates an ECG tracing with the electrical and mechanical events of a heart contraction. Each segment of an ECG tracing corresponds to one event in the cardiac cycle.

Everyday Connection

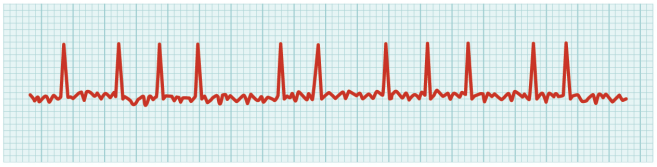
ECG Abnormalities

Occassionally, an area of the heart other than the SA node will initiate an impulse that will be followed by a



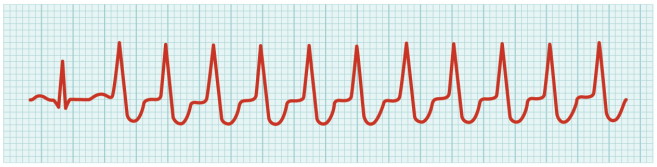
(a) Second-degree (partial) block

Note how half of the P waves are not followed by the QRS complex and T waves while the other half are.
Question: What would you expect to happen to heart rate (pulse)?



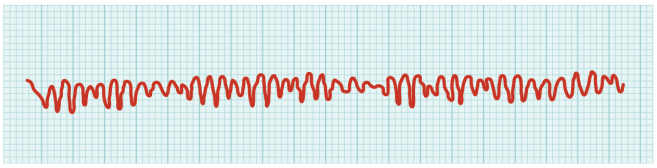
(b) Atrial fibrillation

Note the abnormal electrical pattern prior to the QRS complexes. Also note how the frequency between the QRS complexes has increased.
Question: What would you expect to happen to heart rate (pulse)?



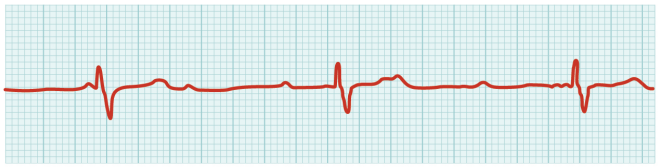
(c) Ventricular tachycardia

Note the unusual shape of the QRS complex, focusing on the "S" component.
Question: What would you expect to happen to heart rate (pulse)?



(d) Ventricular fibrillation

Note the total lack of normal electrical activity.
Question: What would you expect to happen to heart rate (pulse)?



(e) Third-degree block

Note that in a third-degree block some of the impulses initiated by the SA node do not reach the AV node while others do. Also note that the P waves are not followed by the QRS complex.
Question: What would you expect to happen to heart rate (pulse)?

FIGURE 19.25 Common ECG Abnormalities (a) In a second-degree or partial block, one-half of the P waves are not followed by the QRS complex and T waves while the other half are. (b) In atrial fibrillation, the electrical pattern is abnormal prior to the QRS complex, and the frequency between the QRS complexes has increased. (c) In ventricular tachycardia, the shape of the QRS complex is abnormal. (d) In ventricular fibrillation, there is no normal electrical activity. (e) In a third-degree block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex).

INTERACTIVE LINK

Visit this site (http://openstax.org/l/abnormalECG) for a more complete library of abnormal ECGs.

Everyday Connection

External Automated Defibrillators

In the event that the electrical activity of the heart is severely disrupted, cessation of electrical activity or fibrillation may occur. In fibrillation, the heart beats in a wild, uncontrolled manner, which prevents it from being able to pump effectively. Atrial fibrillation (see Figure 19.25**b**) is a serious condition, but as long as the ventricles continue to pump blood, the patient's life may not be in immediate danger. Ventricular fibrillation (see Figure 19.25**d**) is a medical emergency that requires life support, because the ventricles are not effectively pumping blood. In a hospital setting, it is often described as "code blue." If untreated for as little as a few minutes, ventricular fibrillation may lead to brain death. The most common treatment is defibrillation, which uses special paddles to apply a charge to the heart from an external electrical source in an attempt to establish a normal

19.3 Cardiac Cycle

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the relationship between blood pressure and blood flow
- Summarize the events of the cardiac cycle
- Compare atrial and ventricular systole and diastole
- Relate heart sounds detected by auscultation to action of heart's valves

The period of time that begins with contraction of the atria and ends with ventricular relaxation is known as the **cardiac cycle** (Figure 19.27). The period of contraction that the heart undergoes while it pumps blood into circulation is called **systole**. The period of relaxation that occurs as the chambers fill with blood is called **diastole**. Both the atria and ventricles undergo systole and diastole, and it is essential that these components be carefully regulated and coordinated to ensure blood is pumped efficiently to the body.

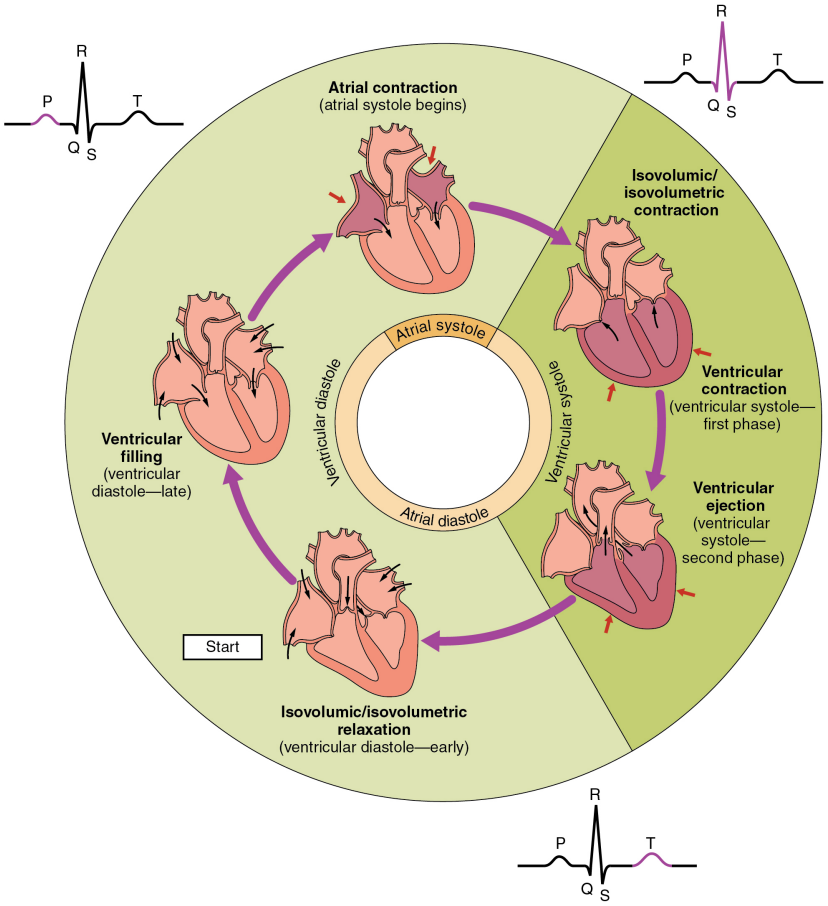


FIGURE 19.27 Overview of the Cardiac Cycle The cardiac cycle begins with atrial systole and progresses to ventricular systole, atrial diastole, and ventricular diastole, when the cycle begins again. Correlations to the ECG are highlighted.

Pressures and Flow

Fluids, whether gases or liquids, are materials that flow according to pressure gradients—that is, they move from regions that are higher in pressure to regions that are lower in pressure. Accordingly, when the heart chambers are relaxed (diastole), blood will flow into the atria from the veins, which are higher in pressure. As blood flows into the atria, the pressure will rise, so the blood will initially move passively from the atria into the ventricles. When the action potential triggers the muscles in the atria to contract (atrial systole), the pressure within the atria rises further, pumping blood into the ventricles. During ventricular systole, pressure rises in the ventricles, pumping blood into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle. Again, as you consider this flow and relate it to the conduction pathway, the elegance of the system should become apparent.

pressure drops within the ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles. Both chambers are in diastole, the atrioventricular valves are open, and the semilunar valves remain closed (see Figure 19.27). The cardiac cycle is complete.

Figure 19.28 illustrates the relationship between the cardiac cycle and the ECG.

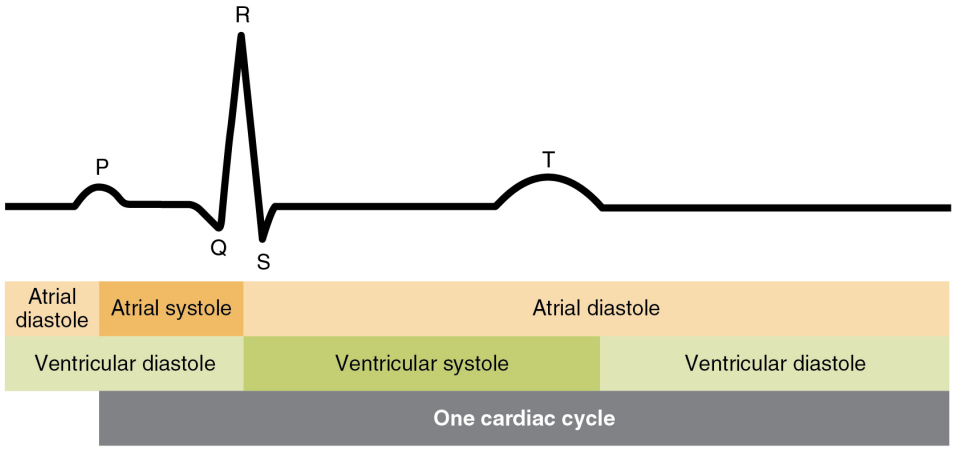


FIGURE 19.28 Relationship between the Cardiac Cycle and ECG Initially, both the atria and ventricles are relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contraction (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS complex represents depolarization of the ventricles and is followed by ventricular contraction. The T wave represents the repolarization of the ventricles and marks the beginning of ventricular relaxation.

Heart Sounds

One of the simplest, yet effective, diagnostic techniques applied to assess the state of a patient's heart is auscultation using a stethoscope.

In a normal, healthy heart, there are only two audible **heart sounds**: S_1 and S_2. S_1 is the sound created by the closing of the atrioventricular valves during ventricular contraction and is normally described as a "lub," or first heart sound. The second heart sound, S_2, is the sound of the closing of the semilunar valves during ventricular diastole and is described as a "dub" (Figure 19.29). In both cases, as the valves close, the openings within the atrioventricular septum guarded by the valves will become reduced, and blood flow through the opening will become more turbulent until the valves are fully closed. There is a third heart sound, S_3, but it is rarely heard in healthy individuals. It may be the sound of blood flowing into the atria, or blood sloshing back and forth in the ventricle, or even tensing of the chordae tendineae. S_3 may be heard in youth, some athletes, and pregnant people. If the sound is heard later in life, it may indicate congestive heart failure, warranting further tests. Some cardiologists refer to the collective S_1, S_2, and S_3 sounds as the "Kentucky gallop," because they mimic those produced by a galloping horse. The fourth heart sound, S_4, results from the contraction of the atria pushing blood into a stiff or hypertrophic ventricle, indicating failure of the left ventricle. S_4 occurs prior to S_1 and the collective sounds S_4, S_1, and S_2 are referred to by some cardiologists as the "Tennessee gallop," because of their similarity to the sound produced by a galloping horse with a different gait. A few individuals may have both S_3 and S_4, and this combined sound is referred to as S_7.

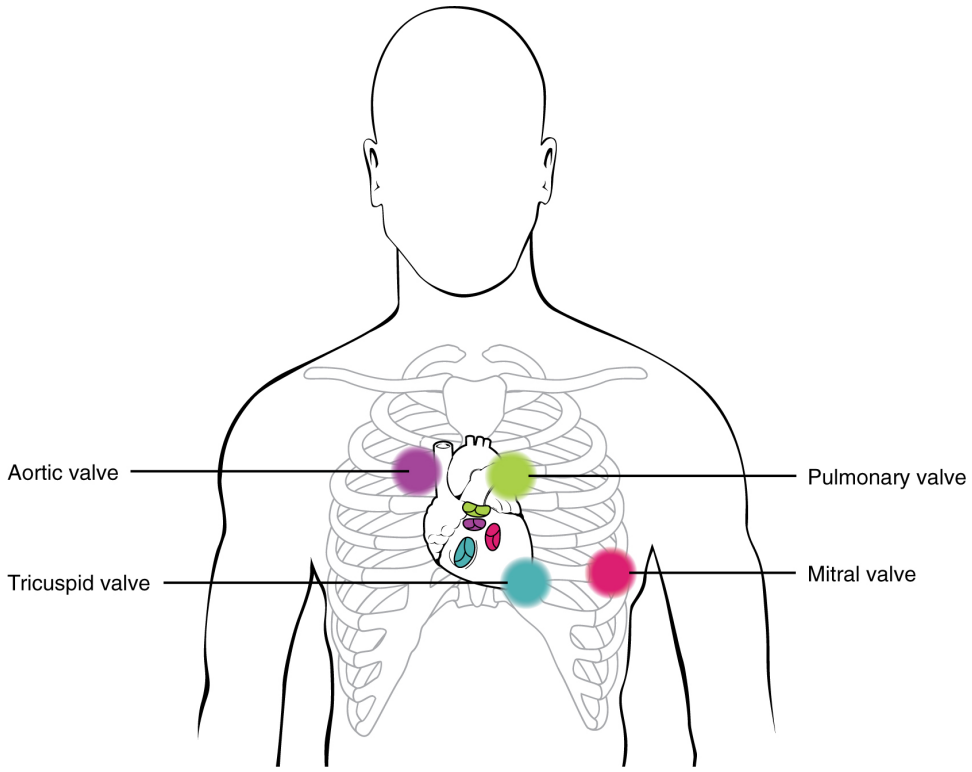


FIGURE 19.30 Stethoscope Placement for Auscultation Proper placement of the bell of the stethoscope facilitates auscultation. At each of the four locations on the chest, a different valve can be heard.

19.4 Cardiac Physiology

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Relate heart rate to cardiac output
- Describe the effect of exercise on heart rate
- Identify cardiovascular centers and cardiac reflexes that regulate heart function
- Describe factors affecting heart rate
- Distinguish between positive and negative factors that affect heart contractility
- Summarize factors affecting stroke volume and cardiac output
- Describe the cardiac response to variations in blood flow and pressure

The autorhythmicity inherent in cardiac cells keeps the heart beating at a regular pace; however, the heart is regulated by and responds to outside influences as well. Neural and endocrine controls are vital to the regulation of cardiac function. In addition, the heart is sensitive to several environmental factors, including electrolytes.

Resting Cardiac Output

Cardiac output (CO) is a measurement of the amount of blood pumped by each ventricle in one minute. To calculate this value, multiply **stroke volume (SV)**, the amount of blood pumped by each ventricle, by **heart rate (HR)**, in contractions per minute (or beats per minute, bpm). It can be represented mathematically by the following equation:

$$CO = HR \times SV$$

SV is normally measured using an echocardiogram to record EDV and ESV, and calculating the difference: SV = EDV – ESV. SV can also be measured using a specialized catheter, but this is an invasive procedure and far more dangerous to the patient. A mean SV for a resting 70-kg (150-lb) individual would be approximately 70 mL. There are several important variables, including size of the heart, physical and mental condition of the individual, sex, contractility, duration of contraction, preload or EDV, and afterload or resistance. Normal range for SV would be 55–100 mL. An average resting HR would be approximately 75 bpm but could range from 60–100 in some

significant. However, if any of these symptoms are present, they may indicate that the heart is not providing sufficient oxygenated blood to the tissues. The term relative bradycardia may be used with a patient who has a HR in the normal range but is still suffering from these symptoms. Most patients remain asymptomatic as long as the HR remains above 50 bpm.

Bradycardia may be caused by either inherent factors or causes external to the heart. While the condition may be inherited, typically it is acquired in older individuals. Inherent causes include abnormalities in either the SA or AV node. If the condition is serious, a pacemaker may be required. Other causes include ischemia to the heart muscle or diseases of the heart vessels or valves. External causes include metabolic disorders, pathologies of the endocrine system often involving the thyroid, electrolyte imbalances, neurological disorders including inappropriate autonomic responses, autoimmune pathologies, over-prescription of beta blocker drugs that reduce HR, recreational drug use, or even prolonged bed rest. Treatment relies upon establishing the underlying cause of the disorder and may necessitate supplemental oxygen.

Tachycardia is not normal in a resting patient but may be detected in pregnant people or individuals experiencing extreme stress. In the latter case, it would likely be triggered by stimulation from the limbic system or disorders of the autonomic nervous system. In some cases, tachycardia may involve only the atria. Some individuals may remain asymptomatic, but when present, symptoms may include dizziness, shortness of breath, lightheadedness, rapid pulse, heart palpations, chest pain, or fainting (syncope). While tachycardia is defined as a HR above 100 bpm, there is considerable variation among people. Further, the normal resting HRs of children are often above 100 bpm, but this is not considered to be tachycardia Many causes of tachycardia may be benign, but the condition may also be correlated with fever, anemia, hypoxia, hyperthyroidism, hypersecretion of catecholamines, some cardiomyopathies, some disorders of the valves, and acute exposure to radiation. Elevated rates in an exercising or resting patient are normal and expected. Resting rate should always be taken after recovery from exercise. Treatment depends upon the underlying cause but may include medications, implantable cardioverter defibrillators, ablation, or surgery.

Correlation Between Heart Rates and Cardiac Output

Initially, physiological conditions that cause HR to increase also trigger an increase in SV. During exercise, the rate of blood returning to the heart increases. However as the HR rises, there is less time spent in diastole and consequently less time for the ventricles to fill with blood. Even though there is less filling time, SV will initially remain high. However, as HR continues to increase, SV gradually decreases due to decreased filling time. CO will initially stabilize as the increasing HR compensates for the decreasing SV, but at very high rates, CO will eventually decrease as increasing rates are no longer able to compensate for the decreasing SV. Consider this phenomenon in a healthy young individual. Initially, as HR increases from resting to approximately 120 bpm, CO will rise. As HR increases from 120 to 160 bpm, CO remains stable, since the increase in rate is offset by decreasing ventricular filling time and, consequently, SV. As HR continues to rise above 160 bpm, CO actually decreases as SV falls faster than HR increases. So although aerobic exercises are critical to maintain the health of the heart, individuals are cautioned to monitor their HR to ensure they stay within the **target heart rate** range of between 120 and 160 bpm, so CO is maintained. The target HR is loosely defined as the range in which both the heart and lungs receive the maximum benefit from the aerobic workout and is dependent upon age.

Cardiovascular Centers

Nervous control over HR is centralized within the two paired cardiovascular centers of the medulla oblongata (Figure 19.32). The cardioaccelerator regions stimulate activity via sympathetic stimulation of the cardioaccelerator nerves, and the cardioinhibitory centers decrease heart activity via parasympathetic stimulation as one component of the vagus nerve, cranial nerve X. During rest, both centers provide slight stimulation to the heart, contributing to **autonomic tone**. This is a similar concept to tone in skeletal muscles. Normally, vagal stimulation predominates as, left unregulated, the SA node would initiate a sinus rhythm of approximately 100 bpm.

Both sympathetic and parasympathetic stimulations flow through a paired complex network of nerve fibers known as the **cardiac plexus** near the base of the heart. The cardioaccelerator center also sends additional fibers, forming the cardiac nerves via sympathetic ganglia (the cervical ganglia plus superior thoracic ganglia T1–T4) to both the SA

increase up to approximately 100 bpm. Any increases beyond this rate would require sympathetic stimulation. Figure 19.33 illustrates the effects of parasympathetic and sympathetic stimulation on the normal sinus rhythm.

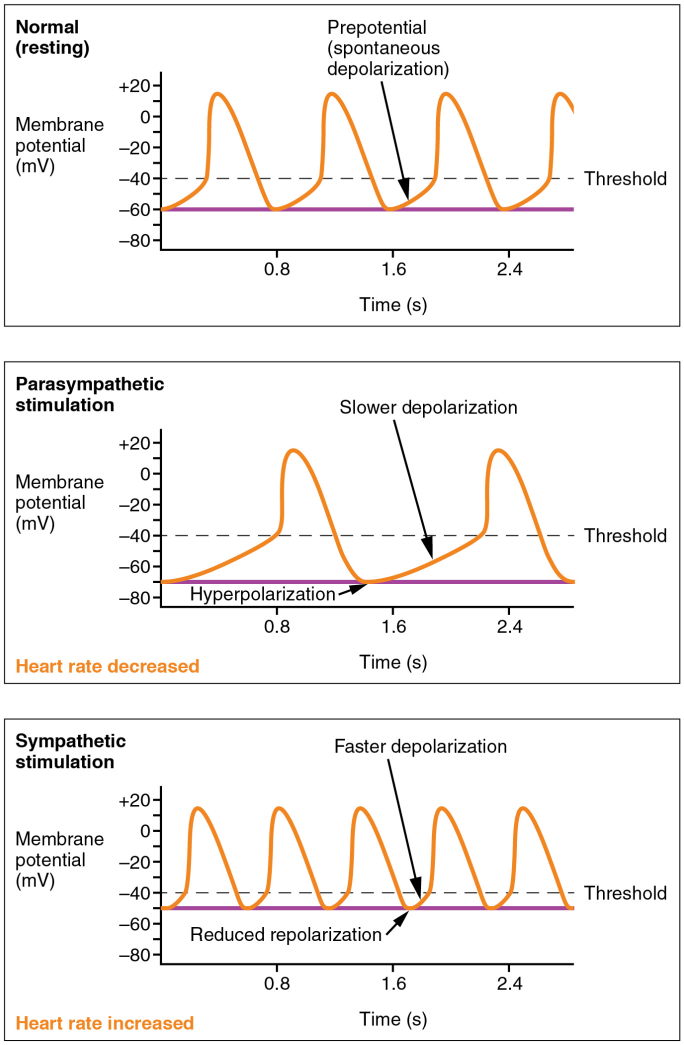


FIGURE 19.33 Effects of Parasympathetic and Sympathetic Stimulation on Normal Sinus Rhythm The wave of depolarization in a normal sinus rhythm shows a stable resting HR. Following parasympathetic stimulation, HR slows. Following sympathetic stimulation, HR increases.

Input to the Cardiovascular Center

The cardiovascular center receives input from a series of visceral receptors with impulses traveling through visceral sensory fibers within the vagus and sympathetic nerves via the cardiac plexus. Among these receptors are various proprioreceptors, baroreceptors, and chemoreceptors, plus stimuli from the limbic system. Collectively, these inputs normally enable the cardiovascular centers to regulate heart function precisely, a process known as **cardiac reflexes**. Increased physical activity results in increased rates of firing by various proprioreceptors located in muscles, joint capsules, and tendons. Any such increase in physical activity would logically warrant increased blood flow. The cardiac centers monitor these increased rates of firing, and suppress parasympathetic stimulation and increase sympathetic stimulation as needed in order to increase blood flow.

Similarly, baroreceptors are stretch receptors located in the aortic sinus, carotid bodies, the venae cavae, and other locations, including pulmonary vessels and the right side of the heart itself. Rates of firing from the baroreceptors represent blood pressure, level of physical activity, and the relative distribution of blood. The cardiac centers monitor baroreceptor firing to maintain cardiac homeostasis, a mechanism called the **baroreceptor reflex**. With increased pressure and stretch, the rate of baroreceptor firing increases, and the cardiac centers decrease sympathetic stimulation and increase parasympathetic stimulation. As pressure and stretch decrease, the rate of

Major Factors Increasing Heart Rate and Force of Contraction

Factor	Effect
Cardioaccelerator nerves	Release of norepinephrine by cardioaccelerator nerves
Proprioreceptors	Increased firing rates of proprioreceptors (e.g. during exercise)
Chemoreceptors	Chemoreceptors sensing decreased levels of O_2 or increased levels of H^+, CO_2 and lactic acid
Baroreceptors	Decreased firing rates of baroreceptors (indicating falling blood volume/pressure)
Limbic system	Anticipation of physical exercise or strong emotions by the limbic system
Catecholamines	Decreased epinephrine and norepinephrine release by the adrenal glands
Thyroid hormones	Increased T_3 and T_4 in the blood (released by thyroid)
Calcium	Decrease in calcium ions in the blood
Potassium	Decrease in potassium ions in the blood
Sodium	Decrease in sodium ions in the blood
Body temperature	Increase in body temperature
Nicotine and caffeine	Presence of nicotine, caffeine or other stimulants

TABLE 19.1

Factors Decreasing Heart Rate and Force of Contraction

Factor	Effect
Cardioinhibitor nerves (vagus)	Release of acetylcholine by cardioinhibitor nerves
Proprioreceptors	Decreased firing rates of proprioreceptors (e.g. during rest)
Chemoreceptors	Chemoreceptors sensing increased levels of O_2 or decreased levels of H^+, CO_2 and lactic acid
Baroreceptors	Increased firing rates of baroreceptors (indicating rising blood volume/pressure)
Limbic system	Anticipation of relaxation by the limbic system
Catecholamines	Decreased epinephrine and norepinephrine release by the adrenal glands

TABLE 19.2

Factors Decreasing Heart Rate

HR can be slowed when a person experiences altered sodium and potassium levels, hypoxia, acidosis, alkalosis, and hypothermia (see Table 19.1). The relationship between electrolytes and HR is complex, but maintaining electrolyte balance is critical to the normal wave of depolarization. Of the two ions, potassium has the greater clinical significance. Initially, both hyponatremia (low sodium levels) and hypernatremia (high sodium levels) may lead to tachycardia. Severely high hypernatremia may lead to fibrillation, which may cause CO to cease. Severe hyponatremia leads to both bradycardia and other arrhythmias. Hypokalemia (low potassium levels) also leads to arrhythmias, whereas hyperkalemia (high potassium levels) causes the heart to become weak and flaccid, and ultimately to fail.

Acidosis is a condition in which excess hydrogen ions are present, and the patient's blood expresses a low pH value. Alkalosis is a condition in which there are too few hydrogen ions, and the patient's blood has an elevated pH. Normal blood pH falls in the range of 7.35–7.45, so a number lower than this range represents acidosis and a higher number represents alkalosis. Recall that enzymes are the regulators or catalysts of virtually all biochemical reactions; they are sensitive to pH and will change shape slightly with values outside their normal range. These variations in pH and accompanying slight physical changes to the active site on the enzyme decrease the rate of formation of the enzyme-substrate complex, subsequently decreasing the rate of many enzymatic reactions, which can have complex effects on HR. Severe changes in pH will lead to denaturation of the enzyme.

The last variable is body temperature. Elevated body temperature is called hyperthermia, and suppressed body temperature is called hypothermia. Slight hyperthermia results in increasing HR and strength of contraction. Hypothermia slows the rate and strength of heart contractions. This distinct slowing of the heart is one component of the larger diving reflex that diverts blood to essential organs while submerged. If sufficiently chilled, the heart will stop beating, a technique that may be employed during open heart surgery. In this case, the patient's blood is normally diverted to an artificial heart-lung machine to maintain the body's blood supply and gas exchange until the surgery is complete, and sinus rhythm can be restored. Excessive hyperthermia and hypothermia will both result in death, as enzymes drive the body systems to cease normal function, beginning with the central nervous system.

Stroke Volume

Many of the same factors that regulate HR also impact cardiac function by altering SV. While a number of variables are involved, SV is ultimately dependent upon the difference between EDV and ESV. The three primary factors to consider are preload, or the stretch on the ventricles prior to contraction; the contractility, or the force or strength of the contraction itself; and afterload, the force the ventricles must generate to pump blood against the resistance in the vessels. These factors are summarized in Table 19.1 and Table 19.2.

Preload

Preload is another way of expressing EDV. Therefore, the greater the EDV is, the greater the preload is. One of the primary factors to consider is **filling time**, or the duration of ventricular diastole during which filling occurs. The more rapidly the heart contracts, the shorter the filling time becomes, and the lower the EDV and preload are. This effect can be partially overcome by increasing the second variable, contractility, and raising SV, but over time, the heart is unable to compensate for decreased filling time, and preload also decreases.

With increasing ventricular filling, both EDV or preload increase, and the cardiac muscle itself is stretched to a greater degree. At rest, there is little stretch of the ventricular muscle, and the sarcomeres remain short. With increased ventricular filling, the ventricular muscle is increasingly stretched and the sarcomere length increases. As the sarcomeres reach their optimal lengths, they will contract more powerfully, because more of the myosin heads can bind to the actin on the thin filaments, forming cross bridges and increasing the strength of contraction and SV. If this process were to continue and the sarcomeres stretched beyond their optimal lengths, the force of contraction would decrease. However, due to the physical constraints of the location of the heart, this excessive stretch is not a concern.

The relationship between ventricular stretch and contraction has been stated in the well-known **Frank-Starling mechanism** or simply Starling's Law of the Heart. This principle states that, within physiological limits, the force of heart contraction is directly proportional to the initial length of the muscle fiber. This means that the greater the stretch of the ventricular muscle (within limits), the more powerful the contraction is, which in turn increases SV. Therefore, by increasing preload, you increase the second variable, contractility.

	Factors Affecting Stroke Volume (SV)		
	Preload	**Contractility**	**Afterload**
Raised due to:	• fast filling time • increased venous return **Increases end diastolic volume,** **Increases stroke volume**	• sympathetic stimulation • epinephrine and norepinephrine • high intracellular calcium ions • high blood calcium level • thyroid hormones • glucagon **Decreases end systolic volume,** **Increases stroke volume**	• increased vascular resistance • semilunar valve damage **Increases end systolic volume** **Decreases stroke volume**
Lowered due to:	• decreased thyroid hormones • decreased calcium ions • high or low potassium ions • high or low sodium • low body temperature • hypoxia • abnormal pH balance • drugs (i.e., calcium channel blockers) **Decreases end diastolic volume,** **Decreases stroke volume**	• parasympathetic stimulation • acetylcholine • hypoxia • hyperkalemia **Increases end systolic volume** **Decreases stroke volume**	• decreased vascular resistance **Decreases end systolic volume** **Increases stroke volume**

FIGURE 19.34 Major Factors Influencing Stroke Volume Multiple factors impact preload, afterload, and contractility, and are the major considerations influencing SV.

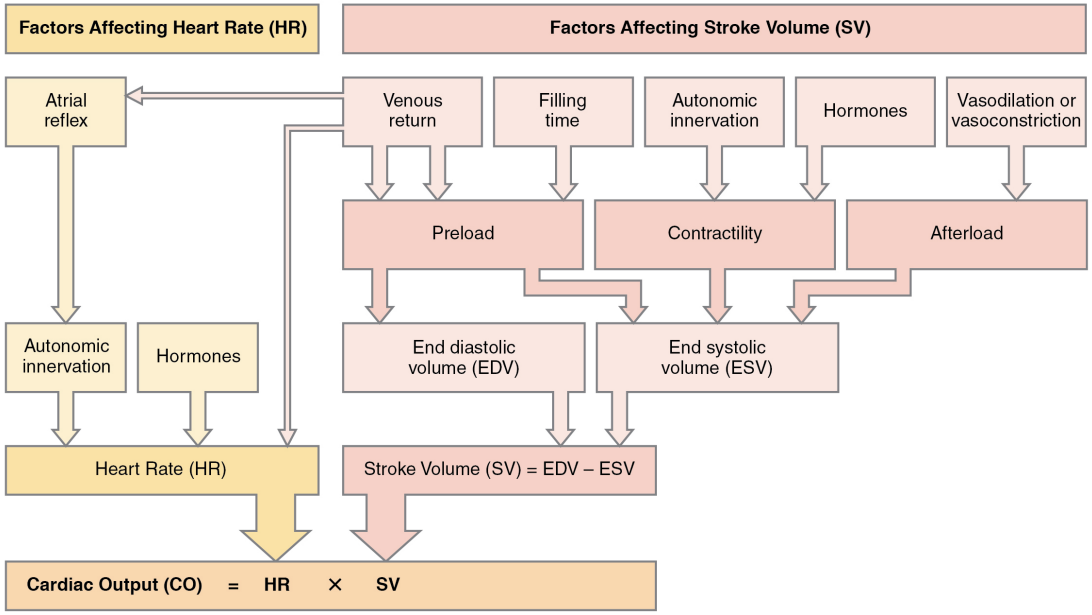


FIGURE 19.35 Summary of Major Factors Influencing Cardiac Output The primary factors influencing HR include autonomic innervation plus endocrine control. Not shown are environmental factors, such as electrolytes, metabolic products, and temperature. The primary factors controlling SV include preload, contractility, and afterload. Other factors such as electrolytes may be classified as either positive or negative inotropic agents.

cardiogenic area. Following chemical signals called factors from the underlying endoderm (another of the three primary germ layers), the cardiogenic area begins to form two strands called the **cardiogenic cords** (Figure 19.36). As the cardiogenic cords develop, a lumen rapidly develops within them. At this point, they are referred to as **endocardial tubes**. The two tubes migrate together and fuse to form a single **primitive heart tube**. The primitive heart tube quickly forms five distinct regions. From head to tail, these include the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and the sinus venosus. Initially, all venous blood flows into the sinus venosus, and contractions propel the blood from tail to head, or from the sinus venosus to the truncus arteriosus. This is a very different pattern from that of an adult.

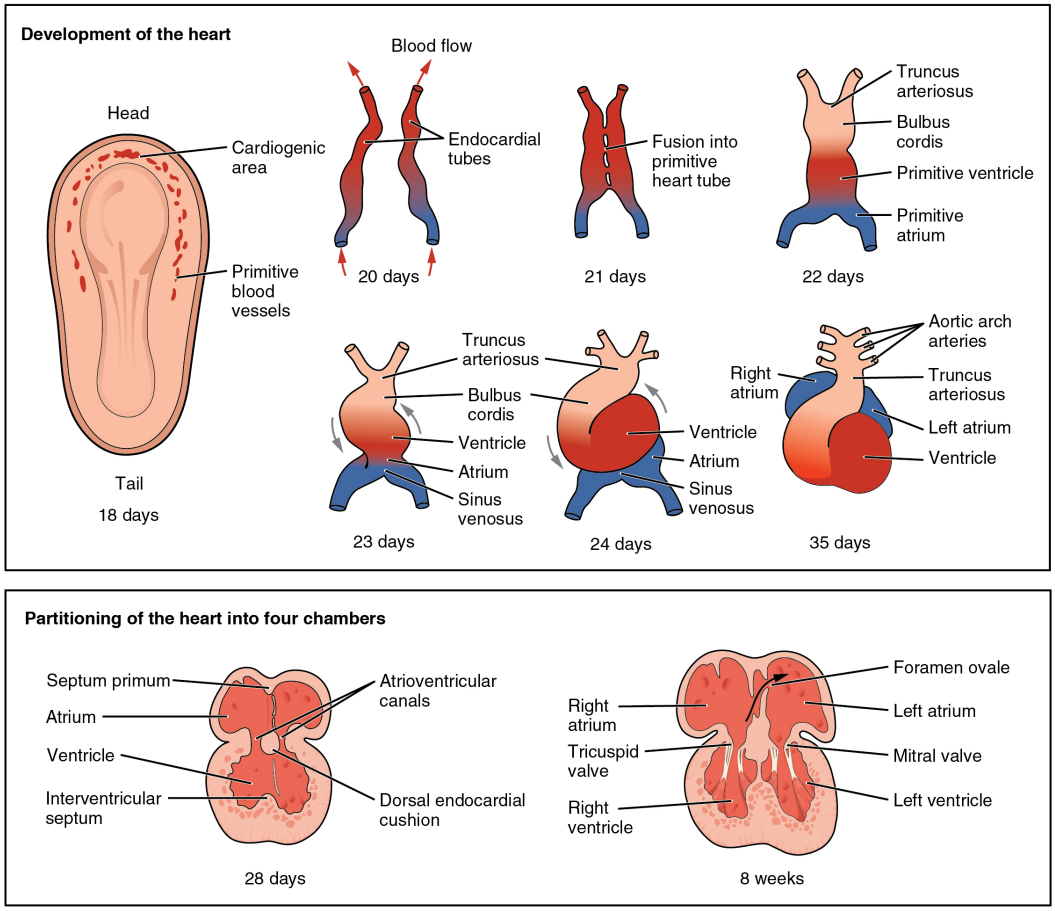


FIGURE 19.36 Development of the Human Heart This diagram outlines the embryological development of the human heart during the first eight weeks and the subsequent formation of the four heart chambers.

The five regions of the primitive heart tube develop into recognizable structures in a fully developed heart. The **truncus arteriosus** will eventually divide and give rise to the ascending aorta and pulmonary trunk. The **bulbus cordis** develops into the right ventricle. The **primitive ventricle** forms the left ventricle. The **primitive atrium** becomes the anterior portions of both the right and left atria, and the two auricles. The **sinus venosus** develops into the posterior portion of the right atrium, the SA node, and the coronary sinus.

As the primitive heart tube elongates, it begins to fold within the pericardium, eventually forming an S shape, which places the chambers and major vessels into an alignment similar to the adult heart. This process occurs between days 23 and 28. The remainder of the heart development pattern includes development of septa and valves, and remodeling of the actual chambers. Partitioning of the atria and ventricles by the interatrial septum, interventricular septum, and atrioventricular septum is complete by the end of the fifth week, although the fetal blood shunts remain until birth or shortly after. The atrioventricular valves form between weeks five and eight, and the semilunar valves form between weeks five and nine.

cardiac reflexes series of autonomic reflexes that enable the cardiovascular centers to regulate heart function based upon sensory information from a variety of visceral sensors

cardiac reserve difference between maximum and resting CO

cardiac skeleton (also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiogenic area area near the head of the embryo where the heart begins to develop 18–19 days after fertilization

cardiogenic cords two strands of tissue that form within the cardiogenic area

cardiomyocyte muscle cell of the heart

chordae tendineae string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

circumflex artery branch of the left coronary artery that follows coronary sulcus

coronary arteries branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus sulcus that marks the boundary between the atria and ventricles

coronary veins vessels that drain the heart and generally parallel the large surface arteries

diastole period of time when the heart muscle is relaxed and the chambers fill with blood

ejection fraction portion of the blood that is pumped or ejected from the heart with each contraction; mathematically represented by SV divided by EDV

electrocardiogram (ECG) surface recording of the electrical activity of the heart that can be used for diagnosis of irregular heart function; also abbreviated as EKG

end diastolic volume (EDV) (also, preload) the amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

end systolic volume (ESV) amount of blood remaining in each ventricle following systole

endocardial tubes stage in which lumens form within the expanding cardiogenic cords, forming hollow structures

endocardium innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endothelium layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

epicardial coronary arteries surface arteries of the heart that generally follow the sulci

epicardium innermost layer of the serous pericardium and the outermost layer of the heart wall

filling time duration of ventricular diastole during which filling occurs

foramen ovale opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

fossa ovalis oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

Frank-Starling mechanism relationship between ventricular stretch and contraction in which the force of heart contraction is directly proportional to the initial length of the muscle fiber

great cardiac vein vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

heart block interruption in the normal conduction pathway

heart bulge prominent feature on the anterior surface of the heart, reflecting early cardiac development

heart rate (HR) number of times the heart contracts (beats) per minute

heart sounds sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves (“lub”) and semilunar valves (“dub”)

hypertrophic cardiomyopathy pathological enlargement of the heart, generally for no known reason

inferior vena cava large systemic vein that returns blood to the heart from the inferior portion of the body

interatrial band (also, Bachmann’s bundle) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

interatrial septum cardiac septum located between

autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

primitive atrium portion of the primitive heart tube that eventually becomes the anterior portions of both the right and left atria, and the two auricles

primitive heart tube singular tubular structure that forms from the fusion of the two endocardial tubes

primitive ventricle portion of the primitive heart tube that eventually forms the left ventricle

pulmonary arteries left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary capillaries capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit blood flow to and from the lungs

pulmonary trunk large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary valve (also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary veins veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

Purkinje fibers specialized myocardial conduction fibers that arise from the bundle branches and spread the impulse to the myocardial contraction fibers of the ventricles

QRS complex component of the electrocardiogram that represents the depolarization of the ventricles and includes, as a component, the repolarization of the atria

right atrioventricular valve (also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

semilunar valves valves located at the base of the pulmonary trunk and at the base of the aorta

septum (plural = septa) walls or partitions that divide the heart into chambers

septum primum flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

sinoatrial (SA) node known as the pacemaker, a specialized clump of myocardial conducting cells located in the superior portion of the right atrium that has the highest inherent rate of depolarization that then spreads throughout the heart

sinus rhythm normal contractile pattern of the heart

sinus venosus develops into the posterior portion of the right atrium, the SA node, and the coronary sinus

small cardiac vein parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the coronary sinus, middle cardiac vein, or right atrium

spontaneous depolarization (also, prepotential depolarization) the mechanism that accounts for the autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

stroke volume (SV) amount of blood pumped by each ventricle per contraction; also, the difference between EDV and ESV

sulcus (plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superior vena cava large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit blood flow to and from virtually all of the tissues of the body

systole period of time when the heart muscle is contracting

T wave component of the electrocardiogram that represents the repolarization of the ventricles

target heart rate range in which both the heart and lungs receive the maximum benefit from an aerobic workout

trabeculae carneae ridges of muscle covered by endocardium located in the ventricles

tricuspid valve term used most often in clinical settings for the right atrioventricular valve

truncus arteriosus portion of the primitive heart that will eventually divide and give rise to the ascending aorta and pulmonary trunk

valve in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

ventricle one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

ventricular ejection phase second phase of

levels, such as the atrial reflex, which is determined by venous return.

SV is regulated by autonomic innervation and hormones, but also by filling time and venous return. Venous return is determined by activity of the skeletal muscles, blood volume, and changes in peripheral circulation. Venous return determines preload and the atrial reflex. Filling time directly related to HR also determines preload. Preload then impacts both EDV and ESV. Autonomic innervation and hormones largely regulate contractility. Contractility impacts EDV as does afterload. CO is the product of HR multiplied by SV. SV is the difference between EDV and ESV.

19.5 Development of the Heart

The heart is the first organ to form and become functional, emphasizing the importance of transport of material to and from the developing infant. It originates about day 18 or 19 from the mesoderm and begins beating and pumping blood about day 21 or 22. It forms from the cardiogenic region near the head and is visible as a prominent heart bulge on the surface of the embryo. Originally, it consists of a pair of strands called cardiogenic cords that quickly form a hollow lumen and are referred to as endocardial tubes. These then fuse into a single heart tube and differentiate into the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus, starting about day 22. The primitive heart begins to form an S shape within the pericardium between days 23 and 28. The internal septa begin to form about day 28, separating the heart into the atria and ventricles, although the foramen ovale persists until shortly after birth. Between weeks five and eight, the atrioventricular valves form. The semilunar valves form between weeks five and nine.

Interactive Link Questions

1. Visit this site (http://openstax.org/l/heartvalve) to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Review Questions

2. Which of the following is not important in preventing backflow of blood?
   a. chordae tendineae
   b. papillary muscles
   c. AV valves
   d. endocardium

3. Which valve separates the left atrium from the left ventricle?
   a. mitral
   b. tricuspid
   c. pulmonary
   d. aortic

4. Which of the following lists the valves in the order through which the blood flows from the vena cava through the heart?
   a. tricuspid, pulmonary semilunar, bicuspid, aortic semilunar
   b. mitral, pulmonary semilunar, bicuspid, aortic semilunar
   c. aortic semilunar, pulmonary semilunar, tricuspid, bicuspid
   d. bicuspid, aortic semilunar, tricuspid, pulmonary semilunar

5. Which chamber initially receives blood from the systemic circuit?
   a. left atrium
   b. left ventricle
   c. right atrium
   d. right ventricle

21. Which of the following is a positive inotrope?
   a. Na^+
   b. K^+
   c. Ca^{2+}
   d. both Na^+ and K^+

22. The earliest organ to form and begin function within the developing human is the _____.
   a. brain
   b. stomach
   c. lungs
   d. heart

23. Of the three germ layers that give rise to all adult tissues and organs, which gives rise to the heart?
   a. ectoderm
   b. endoderm
   c. mesoderm
   d. placenta

24. The two tubes that eventually fuse to form the heart are referred to as the _____.
   a. primitive heart tubes
   b. endocardial tubes
   c. cardiogenic region
   d. cardiogenic tubes

25. Which primitive area of the heart will give rise to the right ventricle?
   a. bulbus cordis
   b. primitive ventricle
   c. sinus venosus
   d. truncus arteriosus

26. The pulmonary trunk and aorta are derived from which primitive heart structure?
   a. bulbus cordis
   b. primitive ventricle
   c. sinus venosus
   d. truncus arteriosus

Critical Thinking Questions

27. Describe how the valves keep the blood moving in one direction.

28. Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

29. Why is the plateau phase so critical to cardiac muscle function?

30. How does the delay of the impulse at the atrioventricular node contribute to cardiac function?

31. How do gap junctions and intercalated disks aid contraction of the heart?

32. Why do the cardiac muscles cells demonstrate autorhythmicity?

33. Describe one cardiac cycle, beginning with both atria and ventricles relaxed.

34. Why does increasing EDV increase contractility?

35. Why is afterload important to cardiac function?

36. Why is it so important for the human heart to develop early and begin functioning within the developing embryo?

37. Describe how the major pumping chambers, the ventricles, form within the developing heart.

20.1 Structure and Function of Blood Vessels

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare and contrast the three tunics that make up the walls of most blood vessels
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function
- Describe the basic structure of a capillary bed, from the supplying metarteriole to the venule into which it drains
- Explain the structure and function of venous valves in the large veins of the extremities

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit (Figure 20.2). Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

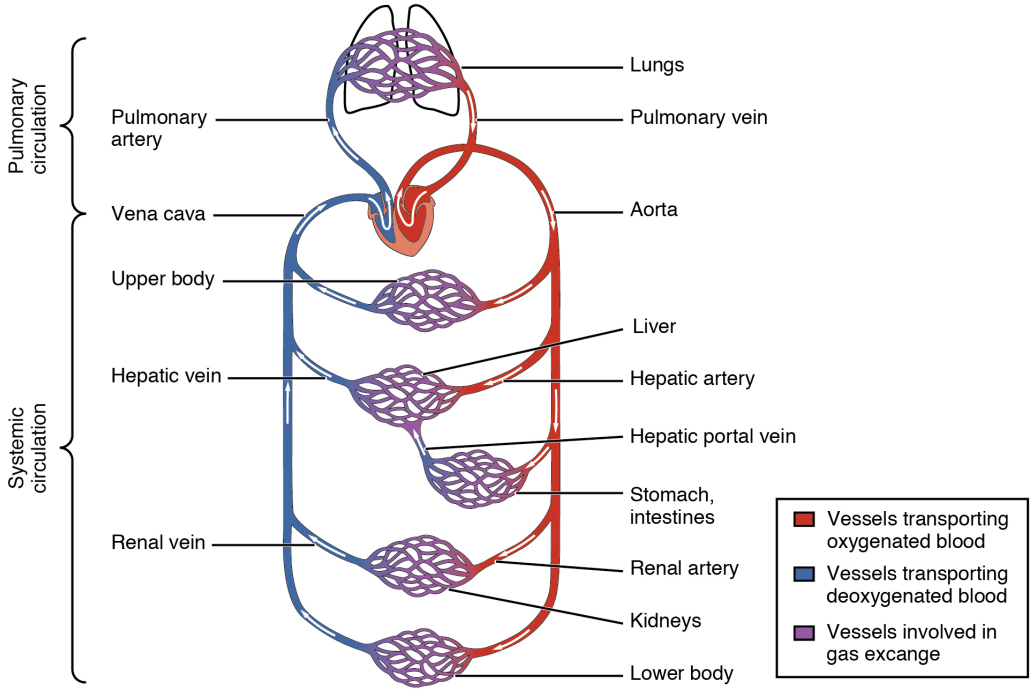


FIGURE 20.2 Cardiovascular Circulation The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure (Figure 20.3). Each type of vessel has a **lumen**—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa (see Figure 20.3). Table 20.1 compares and contrasts the tunics of the arteries and veins.

Comparison of Tunics in Arteries and Veins

	Arteries	Veins
General appearance	Thick walls with small lumens Generally appear rounded	Thin walls with large lumens Generally appear flattened
Tunica intima	Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels	Endothelium appears smooth Internal elastic membrane absent
Tunica media	Normally the thickest layer in arteries Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart) External elastic membrane present in larger vessels	Normally thinner than the tunica externa Smooth muscle cells and collagenous fibers predominate Nervi vasorum and vasa vasorum present External elastic membrane absent
Tunica externa	Normally thinner than the tunica media in all but the largest arteries Collagenous and elastic fibers Nervi vasorum and vasa vasorum present	Normally the thickest layer in veins Collagenous and smooth fibers predominate Some smooth muscle fibers Nervi vasorum and vasa vasorum present

TABLE 20.1

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable,

fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

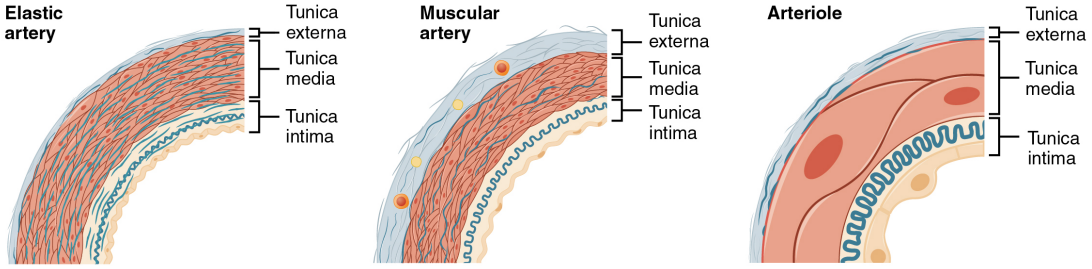


FIGURE 20.4 Types of Arteries and Arterioles Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery's tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see Figure 20.4).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A **capillary** is a microscopic channel that supplies blood to the tissues, a process called **perfusion**. Exchange of gases and other substances occurs between the blood in capillaries and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as **microcirculation**.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional

Metarterioles and Capillary Beds

A **metarteriole** is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more (Figure 20.6). If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a **thoroughfare channel** and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a **vascular shunt**. In addition, an **arteriovenous anastomosis** may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called **vasomotion** and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

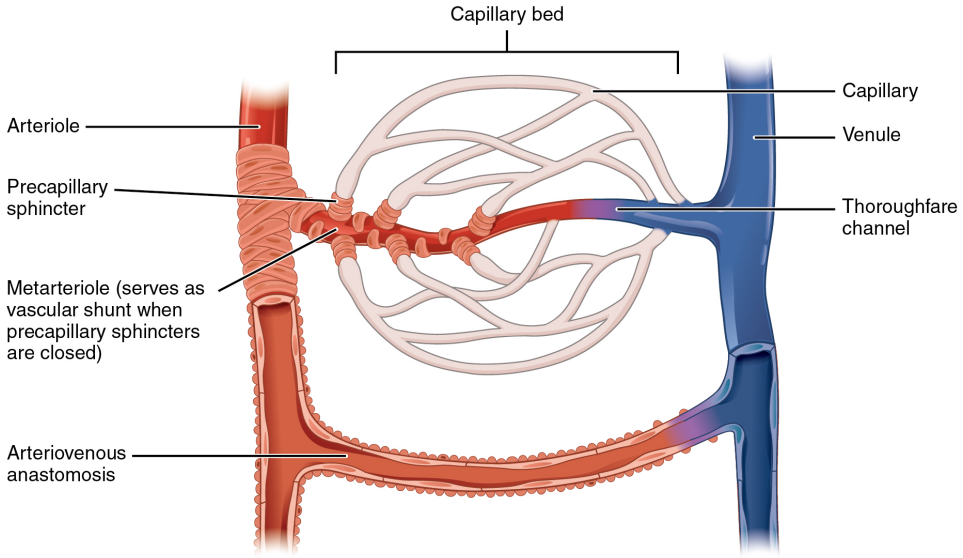


FIGURE 20.6 Capillary Bed In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

Venules

A **venule** is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa (Figure 20.7). Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

	Arteries	Veins
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries Lower in pulmonary arteries	Lower in systemic veins Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

TABLE 20.2

Disorders of the...

Cardiovascular System: Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Systemic circulation 84%	Systemic veins 64%	Large veins 18%
		Large venous networks (liver, bone marrow, and integument) 21%
		Venules and medium-sized veins 25%
	Systemic arteries 13%	Arterioles 2%
		Muscular arteries 5%
		Elastic arteries 4%
		Aorta 2%
	Systemic capillaries 7%	Systemic capillaries 7%
Pulmonary circulation 9%	Pulmonary veins 4%	
	Pulmonary capillaries 2%	
	Pulmonary arteries 3%	
Heart 7%		

FIGURE 20.9 Distribution of Blood Flow

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a "stiffening" of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in Figure 20.9, approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction, this "reserve" volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

CAREER CONNECTION

Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

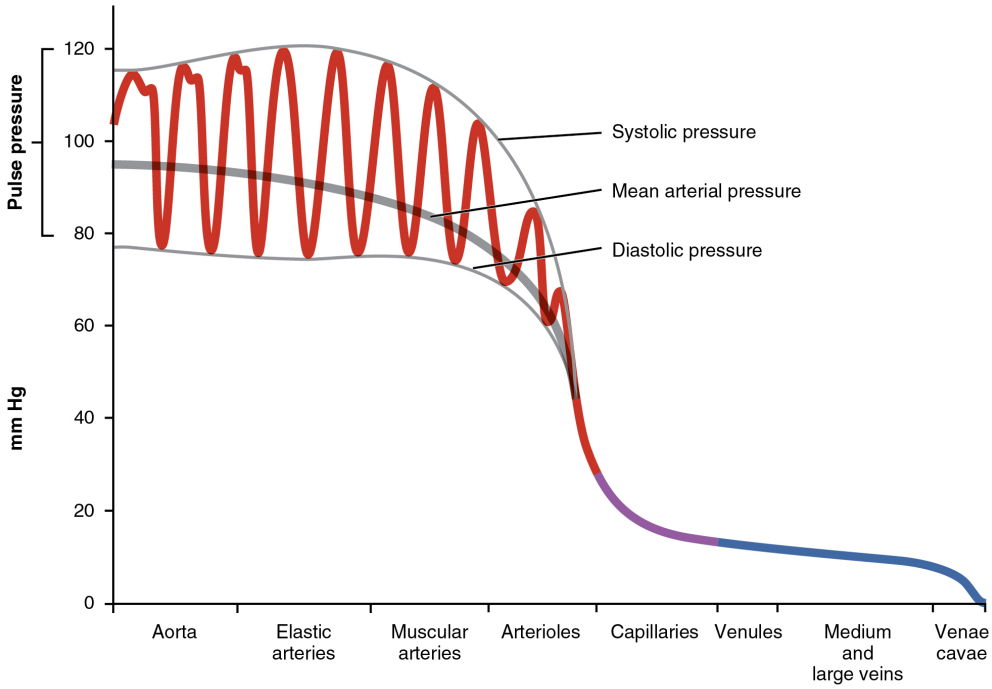


FIGURE 20.10 Systemic Blood Pressure The graph shows the components of blood pressure throughout the blood vessels, including systolic, diastolic, mean arterial, and pulse pressures.

Pulse Pressure

As shown in Figure 20.10, the difference between the systolic pressure and the diastolic pressure is the **pulse pressure**. For example, an individual with a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg would have a pulse pressure of 40 mmHg.

Generally, a pulse pressure should be at least 25 percent of the systolic pressure. A pulse pressure below this level is described as low or narrow. This may occur, for example, in patients with a low stroke volume, which may be seen in congestive heart failure, stenosis of the aortic valve, or significant blood loss following trauma. In contrast, a high or wide pulse pressure is common in healthy people following strenuous exercise, when their resting pulse pressure of 30–40 mm Hg may increase temporarily to 100 mm Hg as stroke volume increases. A persistently high pulse pressure at or above 100 mm Hg may indicate excessive resistance in the arteries and can be caused by a variety of disorders. Chronic high resting pulse pressures can degrade the heart, brain, and kidneys, and warrant medical treatment.

Mean Arterial Pressure

Mean arterial pressure (MAP) represents the "average" pressure of blood in the arteries, that is, the average force driving blood into vessels that serve the tissues. Mean is a statistical concept and is calculated by taking the sum of the values divided by the number of values. Although complicated to measure directly and complicated to calculate, MAP can be approximated by adding the diastolic pressure to one-third of the pulse pressure or systolic pressure minus the diastolic pressure:

$$\text{MAP} = \text{diastolic BP} + \frac{(\text{systolic-diastolic BP})}{3}$$

In Figure 20.10, this value is approximately 80 + (120 – 80) / 3, or 93.33. Normally, the MAP falls within the range of 70–110 mm Hg. If the value falls below 60 mm Hg for an extended time, blood pressure will not be high enough to ensure circulation to and through the tissues, which results in **ischemia**, or insufficient blood flow. A condition called **hypoxia**, inadequate oxygenation of tissues, commonly accompanies ischemia. The term hypoxemia refers to low levels of oxygen in systemic arterial blood. Neurons are especially sensitive to hypoxia and may die or be damaged if blood flow and oxygen supplies are not quickly restored.

Korotkoff. Turbulent blood flow through the vessels can be heard as a soft ticking while measuring blood pressure; these sounds are known as **Korotkoff sounds**. The technique of measuring blood pressure requires the use of a **sphygmomanometer** (a blood pressure cuff attached to a measuring device) and a stethoscope. The technique is as follows:

- The clinician wraps an inflatable cuff tightly around the patient's arm at about the level of the heart.
- The clinician squeezes a rubber pump to inject air into the cuff, raising pressure around the artery and temporarily cutting off blood flow into the patient's arm.
- The clinician places the stethoscope on the patient's antecubital region and, while gradually allowing air within the cuff to escape, listens for the Korotkoff sounds.

Although there are five recognized Korotkoff sounds, only two are normally recorded. Initially, no sounds are heard since there is no blood flow through the vessels, but as air pressure drops, the cuff relaxes, and blood flow returns to the arm. As shown in Figure 20.12, the first sound heard through the stethoscope—the first Korotkoff sound—indicates systolic pressure. As more air is released from the cuff, blood is able to flow freely through the brachial artery and all sounds disappear. The point at which the last sound is heard is recorded as the patient's diastolic pressure.

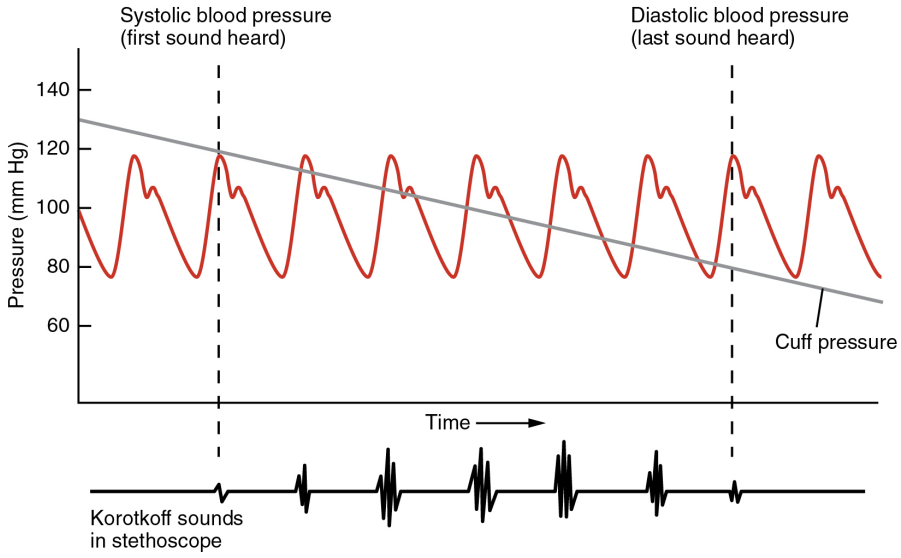


FIGURE 20.12 Blood Pressure Measurement When pressure in a sphygmomanometer cuff is released, a clinician can hear the Korotkoff sounds. In this graph, a blood pressure tracing is aligned to a measurement of systolic and diastolic pressures.

The majority of hospitals and clinics have automated equipment for measuring blood pressure that work on the same principles. An even more recent innovation is a small instrument that wraps around a patient's wrist. The patient then holds the wrist over the heart while the device measures blood flow and records pressure.

Variables Affecting Blood Flow and Blood Pressure

Five variables influence blood flow and blood pressure:

- Cardiac output
- Compliance
- Volume of the blood
- Viscosity of the blood
- Blood vessel length and diameter

Recall that blood moves from higher pressure to lower pressure. It is pumped from the heart into the arteries at high pressure. If you increase pressure in the arteries (afterload), and cardiac function does not compensate, blood flow will actually decrease. In the venous system, the opposite relationship is true. Increased pressure in the veins does not decrease flow as it does in arteries, but actually increases flow. Since pressure in the veins is normally relatively low, for blood to flow back into the heart, the pressure in the atria during atrial diastole must be even lower. It normally approaches zero, except when the atria contract (see Figure 20.10).

what they can teach us about the impact on blood flow.

Blood Volume

The relationship between blood volume, blood pressure, and blood flow is intuitively obvious. Water may merely trickle along a creek bed in a dry season, but rush quickly and under great pressure after a heavy rain. Similarly, as blood volume decreases, pressure and flow decrease. As blood volume increases, pressure and flow increase.

Under normal circumstances, blood volume varies little. Low blood volume, called **hypovolemia**, may be caused by bleeding, dehydration, vomiting, severe burns, or some medications used to treat hypertension. It is important to recognize that other regulatory mechanisms in the body are so effective at maintaining blood pressure that an individual may be asymptomatic until 10–20 percent of the blood volume has been lost. Treatment typically includes intravenous fluid replacement.

Hypervolemia, excessive fluid volume, may be caused by retention of water and sodium, as seen in patients with heart failure, liver cirrhosis, some forms of kidney disease, hyperaldosteronism, and some glucocorticoid steroid treatments. Restoring homeostasis in these patients depends upon reversing the condition that triggered the hypervolemia.

Blood Viscosity

Viscosity is the thickness of fluids that affects their ability to flow. Clean water, for example, is less viscous than mud. The viscosity of blood is directly proportional to resistance and inversely proportional to flow; therefore, any condition that causes viscosity to increase will also increase resistance and decrease flow. For example, imagine sipping milk, then a milkshake, through the same size straw. You experience more resistance and therefore less flow from the milkshake. Conversely, any condition that causes viscosity to decrease (such as when the milkshake melts) will decrease resistance and increase flow.

Normally the viscosity of blood does not change over short periods of time. The two primary determinants of blood viscosity are the formed elements and plasma proteins. Since the vast majority of formed elements are erythrocytes, any condition affecting erythropoiesis, such as polycythemia or anemia, can alter viscosity. Since most plasma proteins are produced by the liver, any condition affecting liver function can also change the viscosity slightly and therefore alter blood flow. Liver abnormalities such as hepatitis, cirrhosis, alcohol damage, and drug toxicities result in decreased levels of plasma proteins, which decrease blood viscosity. While leukocytes and platelets are normally a small component of the formed elements, there are some rare conditions in which severe overproduction can impact viscosity as well.

Vessel Length and Diameter

The length of a vessel is directly proportional to its resistance: the longer the vessel, the greater the resistance and the lower the flow. As with blood volume, this makes intuitive sense, since the increased surface area of the vessel will impede the flow of blood. Likewise, if the vessel is shortened, the resistance will decrease and flow will increase.

The length of our blood vessels increases throughout childhood as we grow, of course, but is unchanging in adults under normal physiological circumstances. Further, the distribution of vessels is not the same in all tissues. Adipose tissue does not have an extensive vascular supply. One pound of adipose tissue contains approximately 200 miles of vessels, whereas skeletal muscle contains more than twice that. Overall, vessels decrease in length only during loss of mass or amputation. An individual weighing 150 pounds has approximately 60,000 miles of vessels in the body. Gaining about 10 pounds adds from 2000 to 4000 miles of vessels, depending upon the nature of the gained tissue. One of the great benefits of weight reduction is the reduced stress to the heart, which does not have to overcome the resistance of as many miles of vessels.

In contrast to length, the diameter of blood vessels changes throughout the body, according to the type of vessel, as we discussed earlier. The diameter of any given vessel may also change frequently throughout the day in response to neural and chemical signals that trigger vasodilation and vasoconstriction. The **vascular tone** of the vessel is the contractile state of the smooth muscle and the primary determinant of diameter, and thus of resistance and flow. The effect of vessel diameter on resistance is inverse: Given the same volume of blood, an increased diameter means there is less blood contacting the vessel wall, thus lower friction and lower resistance, subsequently increasing flow. A decreased diameter means more of the blood contacts the vessel wall, and resistance increases,

Disorders of the...

Cardiovascular System: Arteriosclerosis

Compliance allows an artery to expand when blood is pumped through it from the heart, and then to recoil after the surge has passed. This helps promote blood flow. In arteriosclerosis, compliance is reduced, and pressure and resistance within the vessel increase. This is a leading cause of hypertension and coronary heart disease, as it causes the heart to work harder to generate a pressure great enough to overcome the resistance.

Arteriosclerosis begins with injury to the endothelium of an artery, which may be caused by irritation from high blood glucose, infection, tobacco use, excessive blood lipids, and other factors. Artery walls that are constantly stressed by blood flowing at high pressure are also more likely to be injured—which means that hypertension can promote arteriosclerosis, as well as result from it.

Recall that tissue injury causes inflammation. As inflammation spreads into the artery wall, it weakens and scars it, leaving it stiff (sclerotic). As a result, compliance is reduced. Moreover, circulating triglycerides and cholesterol can seep between the damaged lining cells and become trapped within the artery wall, where they are frequently joined by leukocytes, calcium, and cellular debris. Eventually, this buildup, called plaque, can narrow arteries enough to impair blood flow. The term for this condition, atherosclerosis (athero- = "porridge") describes the mealy deposits (Figure 20.14).

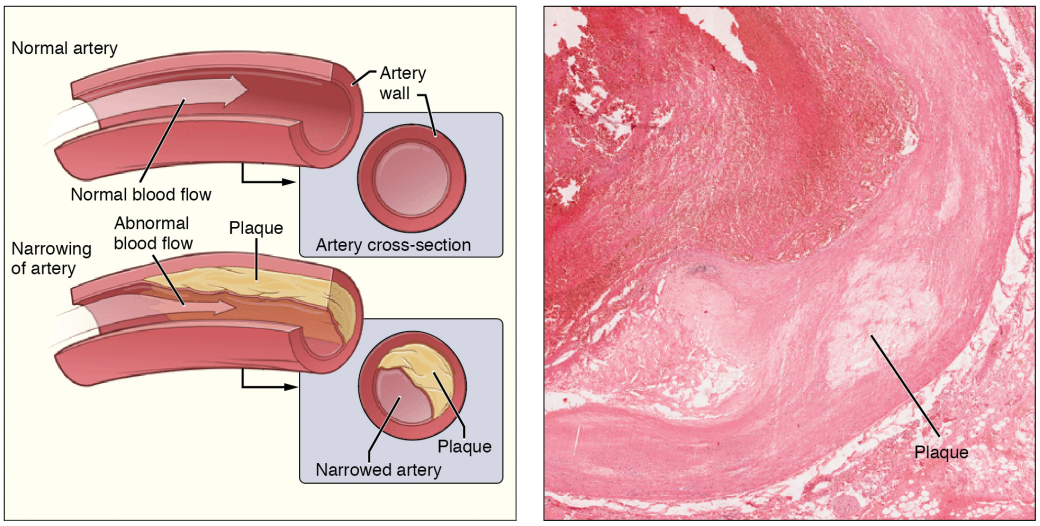


FIGURE 20.14 Atherosclerosis (a) Atherosclerosis can result from plaques formed by the buildup of fatty, calcified deposits in an artery. (b) Plaques can also take other forms, as shown in this micrograph of a coronary artery that has a buildup of connective tissue within the artery wall. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Sometimes a plaque can rupture, causing microscopic tears in the artery wall that allow blood to leak into the tissue on the other side. When this happens, platelets rush to the site to clot the blood. This clot can further obstruct the artery and—if it occurs in a coronary or cerebral artery—cause a sudden heart attack or stroke. Alternatively, plaque can break off and travel through the bloodstream as an embolus until it blocks a more distant, smaller artery.

Even without total blockage, vessel narrowing leads to ischemia—reduced blood flow—to the tissue region "downstream" of the narrowed vessel. Ischemia in turn leads to hypoxia—decreased supply of oxygen to the tissues. Hypoxia involving cardiac muscle or brain tissue can lead to cell death and severe impairment of brain or heart function.

A major risk factor for both arteriosclerosis and atherosclerosis is advanced age, as the conditions tend to progress over time. Arteriosclerosis is normally defined as the more generalized loss of compliance, "hardening of the arteries," whereas atherosclerosis is a more specific term for the build-up of plaque in the walls of the vessel and is a specific type of arteriosclerosis. There is also a distinct genetic component, and pre-existing

valves to assure that blood flows only in the proper direction.

Respiratory Pump

The **respiratory pump** aids blood flow through the veins of the thorax and abdomen. During inhalation, the volume of the thorax increases, largely through the contraction of the diaphragm, which moves downward and compresses the abdominal cavity. The elevation of the chest caused by the contraction of the external intercostal muscles also contributes to the increased volume of the thorax. The volume increase causes air pressure within the thorax to decrease, allowing us to inhale. Additionally, as air pressure within the thorax drops, blood pressure in the thoracic veins also decreases, falling below the pressure in the abdominal veins. This causes blood to flow along its pressure gradient from veins outside the thorax, where pressure is higher, into the thoracic region, where pressure is now lower. This in turn promotes the return of blood from the thoracic veins to the atria. During exhalation, when air pressure increases within the thoracic cavity, pressure in the thoracic veins increases, speeding blood flow into the heart while valves in the veins prevent blood from flowing backward from the thoracic and abdominal veins.

Pressure Relationships in the Venous System

Although vessel diameter increases from the smaller venules to the larger veins and eventually to the venae cavae (singular = vena cava), the total cross-sectional area actually decreases (see Figure 20.15**a** and **b**). The individual veins are larger in diameter than the venules, but their total number is much lower, so their total cross-sectional area is also lower.

Also notice that, as blood moves from venules to veins, the average blood pressure drops (see Figure 20.15**c**), but the blood velocity actually increases (see Figure 20.15). This pressure gradient drives blood back toward the heart. Again, the presence of one-way valves and the skeletal muscle and respiratory pumps contribute to this increased flow. Since approximately 64 percent of the total blood volume resides in systemic veins, any action that increases the flow of blood through the veins will increase venous return to the heart. Maintaining vascular tone within the veins prevents the veins from merely distending, dampening the flow of blood, and as you will see, vasoconstriction actually enhances the flow.

The Role of Venoconstriction in Resistance, Blood Pressure, and Flow

As previously discussed, vasoconstriction of an artery or arteriole decreases the radius, increasing resistance and pressure, but decreasing flow. Venoconstriction, on the other hand, has a very different outcome. The walls of veins are thin but irregular; thus, when the smooth muscle in those walls constricts, the lumen becomes more rounded. The more rounded the lumen, the less surface area the blood encounters, and the less resistance the vessel offers. Vasoconstriction increases pressure within a vein as it does in an artery, but in veins, the increased pressure increases flow. Recall that the pressure in the atria, into which the venous blood will flow, is very low, approaching zero for at least part of the relaxation phase of the cardiac cycle. Thus, venoconstriction increases the return of blood to the heart. Another way of stating this is that venoconstriction increases the preload or stretch of the cardiac muscle and increases contraction.

20.3 Capillary Exchange

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the primary mechanisms of capillary exchange
- Distinguish between capillary hydrostatic pressure and blood colloid osmotic pressure, explaining the contribution of each to net filtration pressure
- Compare filtration and reabsorption
- Explain the fate of fluid that is not reabsorbed from the tissues into the vascular capillaries

The primary purpose of the cardiovascular system is to circulate gases, nutrients, wastes, and other substances to and from the cells of the body. Small molecules, such as gases, lipids, and lipid-soluble molecules, can diffuse directly through the membranes of the endothelial cells of the capillary wall. Glucose, amino acids, and ions—including sodium, potassium, calcium, and chloride—use transporters to move through specific channels in the membrane by facilitated diffusion. Glucose, ions, and larger molecules may also leave the blood through intercellular clefts. Larger molecules can pass through the pores of fenestrated capillaries, and even large plasma proteins can pass through the great gaps in the sinusoids. Some large proteins in blood plasma can move into and

out of the capillary. It is equal to the difference between the CHP and the BCOP. Since filtration is, by definition, the movement of fluid out of the capillary, when reabsorption is occurring, the NFP is a negative number.

NFP changes at different points in a capillary bed (Figure 20.16). Close to the arterial end of the capillary, it is approximately 10 mm Hg, because the CHP of 35 mm Hg minus the BCOP of 25 mm Hg equals 10 mm Hg. Recall that the hydrostatic and osmotic pressures of the interstitial fluid are essentially negligible. Thus, the NFP of 10 mm Hg drives a net movement of fluid out of the capillary at the arterial end. At approximately the middle of the capillary, the CHP is about the same as the BCOP of 25 mm Hg, so the NFP drops to zero. At this point, there is no net change of volume: Fluid moves out of the capillary at the same rate as it moves into the capillary. Near the venous end of the capillary, the CHP has dwindled to about 18 mm Hg due to loss of fluid. Because the BCOP remains steady at 25 mm Hg, water is drawn into the capillary, that is, reabsorption occurs. Another way of expressing this is to say that at the venous end of the capillary, there is an NFP of –7 mm Hg.

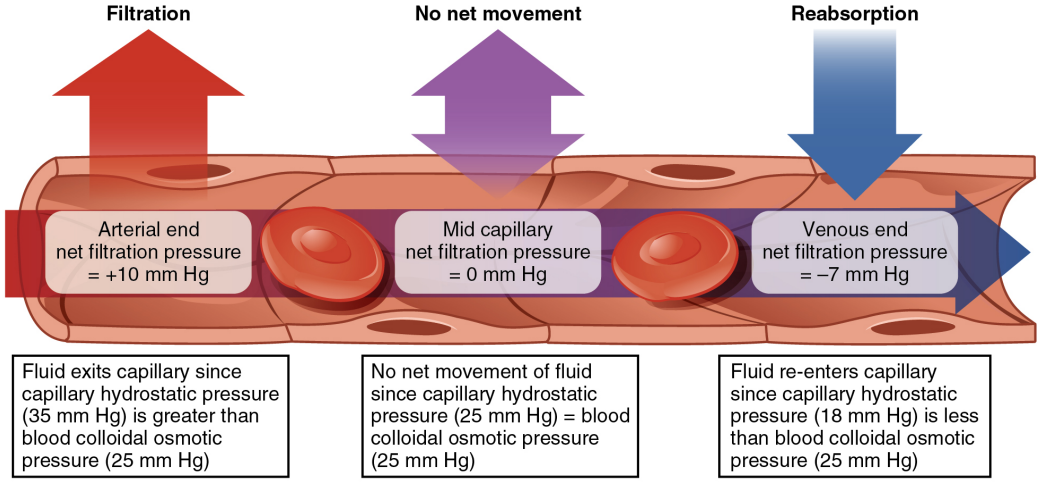


FIGURE 20.16 Capillary Exchange Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint since CHP = BCOP. Net reabsorption occurs near the venous end since BCOP is greater than CHP.

The Role of Lymphatic Capillaries

Since overall CHP is higher than BCOP, it is inevitable that more net fluid will exit the capillary through filtration at the arterial end than enters through reabsorption at the venous end. Considering all capillaries over the course of a day, this can be quite a substantial amount of fluid: Approximately 24 liters per day are filtered, whereas 20.4 liters are reabsorbed. This excess fluid is picked up by capillaries of the lymphatic system. These extremely thin-walled vessels have copious numbers of valves that ensure unidirectional flow through ever-larger lymphatic vessels that eventually drain into the subclavian veins in the neck. An important function of the lymphatic system is to return the fluid (lymph) to the blood. Lymph may be thought of as recycled blood plasma. (Seek additional content for more detail on the lymphatic system.)

INTERACTIVE LINK

Watch this video (http://openstax.org/l/capillaryfunct) to explore capillaries and how they function in the body. Capillaries are never more than 100 micrometers away. What is the main component of interstitial fluid?

20.4 Homeostatic Regulation of the Vascular System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the mechanisms involved in the neural regulation of vascular homeostasis
- Describe the contribution of a variety of hormones to the renal regulation of blood pressure
- Identify the effects of exercise on vascular homeostasis
- Discuss how hypertension, hemorrhage, and circulatory shock affect vascular health

In order to maintain homeostasis in the cardiovascular system and provide adequate blood to the tissues, blood

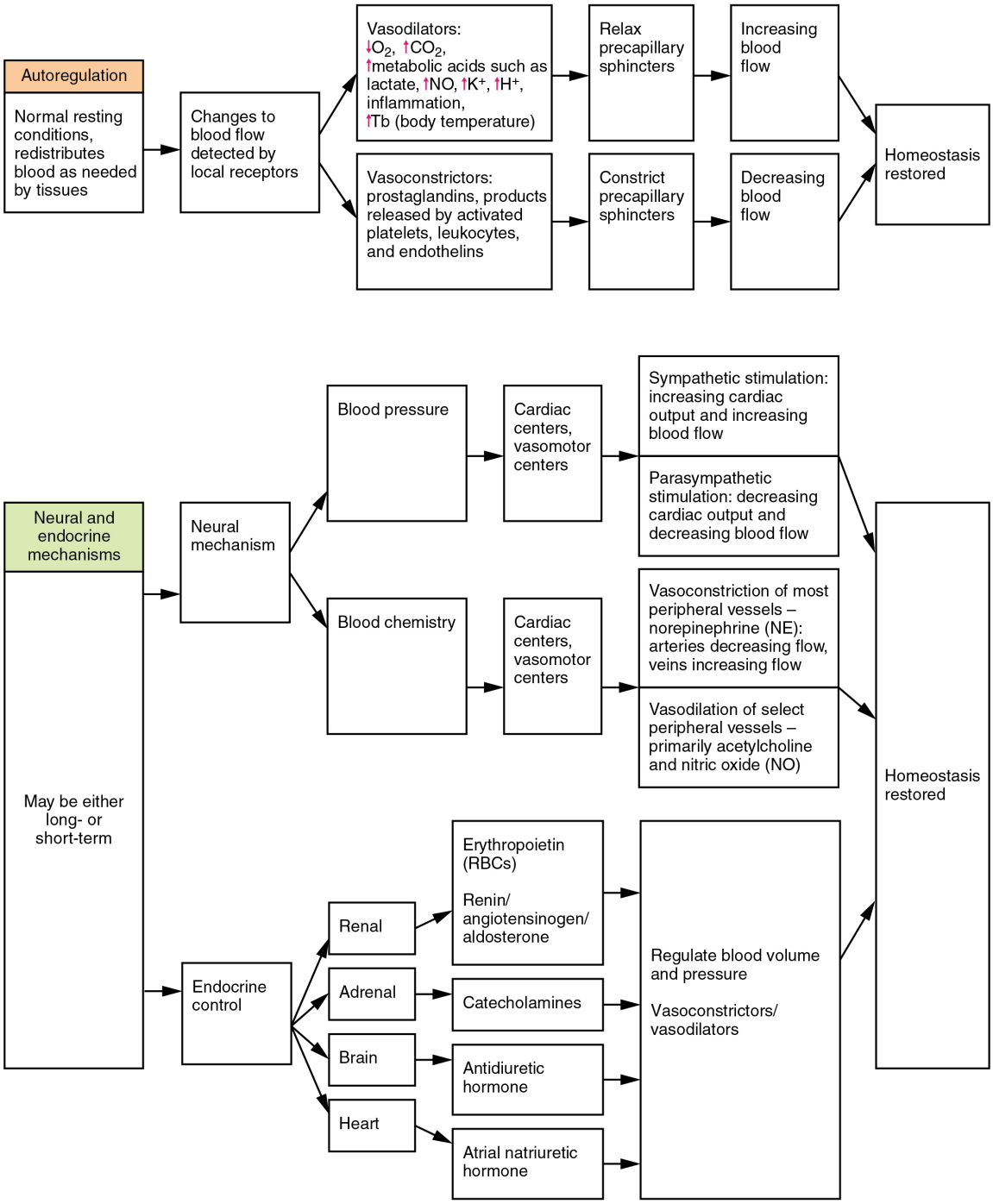


FIGURE 20.17 Summary of Factors Maintaining Vascular Homeostasis Adequate blood flow, blood pressure, distribution, and perfusion involve autoregulatory, neural, and endocrine mechanisms.

Neural Regulation

The nervous system plays a critical role in the regulation of vascular homeostasis. The primary regulatory sites include the cardiovascular centers in the brain that control both cardiac and vascular functions. In addition, more generalized neural responses from the limbic system and the autonomic nervous system are factors.

The Cardiovascular Centers in the Brain

Neurological regulation of blood pressure and flow depends on the cardiovascular centers located in the medulla oblongata. This cluster of neurons responds to changes in blood pressure as well as blood concentrations of oxygen, carbon dioxide, and hydrogen ions. The cardiovascular center contains three distinct paired components:

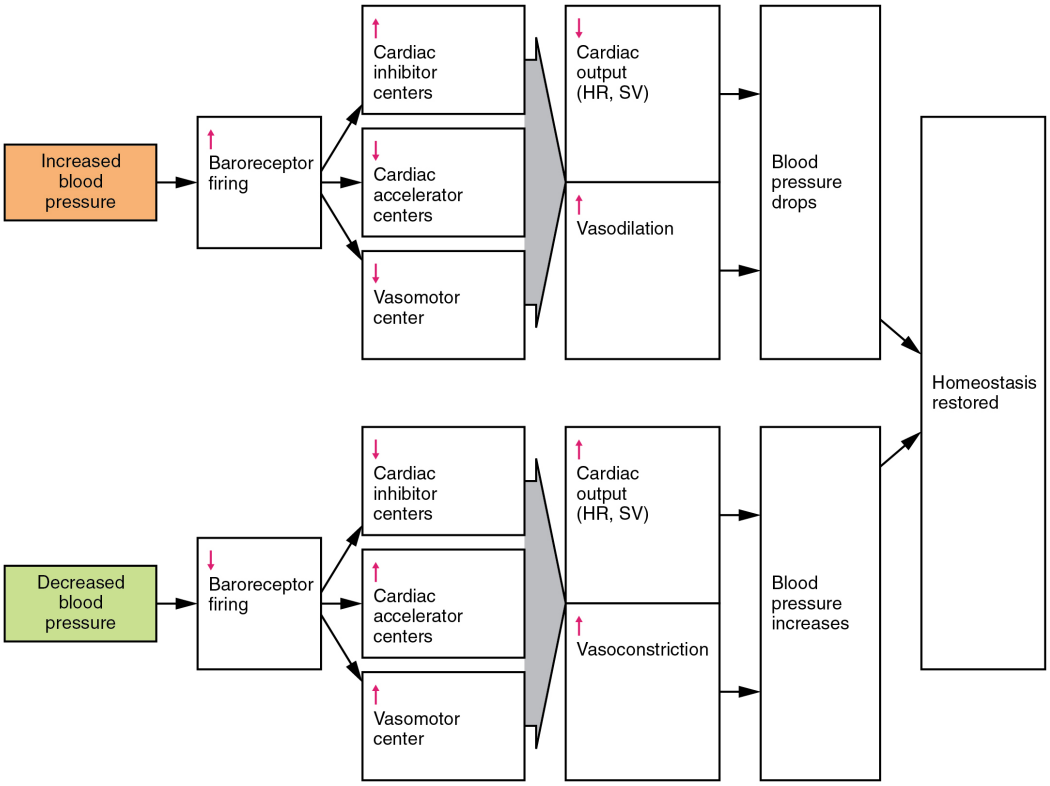


FIGURE 20.18 Baroreceptor Reflexes for Maintaining Vascular Homeostasis Increased blood pressure results in increased rates of baroreceptor firing, whereas decreased blood pressure results in slower rates of fire, both initiating the homeostatic mechanism to restore blood pressure.

The baroreceptors in the venae cavae and right atrium monitor blood pressure as the blood returns to the heart from the systemic circulation. Normally, blood flow into the aorta is the same as blood flow back into the right atrium. If blood is returning to the right atrium more rapidly than it is being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until homeostasis is achieved. The opposite is also true. This mechanism is referred to as the **atrial reflex**.

Chemoreceptor Reflexes

In addition to the baroreceptors are chemoreceptors that monitor levels of oxygen, carbon dioxide, and hydrogen ions (pH), and thereby contribute to vascular homeostasis. Chemoreceptors monitoring the blood are located in close proximity to the baroreceptors in the aortic and carotid sinuses. They signal the cardiovascular center as well as the respiratory centers in the medulla oblongata.

Since tissues consume oxygen and produce carbon dioxide and acids as waste products, when the body is more active, oxygen levels fall and carbon dioxide levels rise as cells undergo cellular respiration to meet the energy needs of activities. This causes more hydrogen ions to be produced, causing the blood pH to drop. When the body is resting, oxygen levels are higher, carbon dioxide levels are lower, more hydrogen is bound, and pH rises. (Seek additional content for more detail about pH.)

The chemoreceptors respond to increasing carbon dioxide and hydrogen ion levels (falling pH) by stimulating the cardioaccelerator and vasomotor centers, increasing cardiac output and constricting peripheral vessels. The cardioinhibitor centers are suppressed. With falling carbon dioxide and hydrogen ion levels (increasing pH), the cardioinhibitor centers are stimulated, and the cardioaccelerator and vasomotor centers are suppressed, decreasing cardiac output and causing peripheral vasodilation. In order to maintain adequate supplies of oxygen to the cells and remove waste products such as carbon dioxide, it is essential that the respiratory system respond to changing metabolic demands. In turn, the cardiovascular system will transport these gases to the lungs for exchange, again in accordance with metabolic demands. This interrelationship of cardiovascular and respiratory control cannot be overemphasized.

Other neural mechanisms can also have a significant impact on cardiovascular function. These include the limbic

production of erythrocytes within the bone marrow. Erythrocytes are the major formed element of the blood and may contribute 40 percent or more to blood volume, a significant factor of viscosity, resistance, pressure, and flow. In addition, EPO is a vasoconstrictor. Overproduction of EPO or excessive intake of synthetic EPO, often to enhance athletic performance, will increase viscosity, resistance, and pressure, and decrease flow in addition to its contribution as a vasoconstrictor.

Atrial Natriuretic Hormone

Secreted by cells in the atria of the heart, atrial natriuretic hormone (ANH) (also known as atrial natriuretic peptide) is secreted when blood volume is high enough to cause extreme stretching of the cardiac cells. Cells in the ventricle produce a hormone with similar effects, called B-type natriuretic hormone. Natriuretic hormones are antagonists to angiotensin II. They promote loss of sodium and water from the kidneys, and suppress renin, aldosterone, and ADH production and release. All of these actions promote loss of fluid from the body, so blood volume and blood pressure drop.

Autoregulation of Perfusion

As the name would suggest, autoregulation mechanisms require neither specialized nervous stimulation nor endocrine control. Rather, these are local, self-regulatory mechanisms that allow each region of tissue to adjust its blood flow—and thus its perfusion. These local mechanisms include chemical signals and myogenic controls.

Chemical Signals Involved in Autoregulation

Chemical signals work at the level of the precapillary sphincters to trigger either constriction or relaxation. As you know, opening a precapillary sphincter allows blood to flow into that particular capillary, whereas constricting a precapillary sphincter temporarily shuts off blood flow to that region. The factors involved in regulating the precapillary sphincters include the following:

- Opening of the sphincter is triggered in response to decreased oxygen concentrations; increased carbon dioxide concentrations; increasing levels of lactic acid or other byproducts of cellular metabolism; increasing concentrations of potassium ions or hydrogen ions (falling pH); inflammatory chemicals such as histamines; and increased body temperature. These conditions in turn stimulate the release of NO, a powerful vasodilator, from endothelial cells (see Figure 20.17).
- Contraction of the precapillary sphincter is triggered by the opposite levels of the regulators, which prompt the release of endothelins, powerful vasoconstricting peptides secreted by endothelial cells. Platelet secretions and certain prostaglandins may also trigger constriction.

Again, these factors alter tissue perfusion via their effects on the precapillary sphincter mechanism, which regulates blood flow to capillaries. Since the amount of blood is limited, not all capillaries can fill at once, so blood flow is allocated based upon the needs and metabolic state of the tissues as reflected in these parameters. Bear in mind, however, that dilation and constriction of the arterioles feeding the capillary beds is the primary control mechanism.

The Myogenic Response

The **myogenic response** is a reaction to the stretching of the smooth muscle in the walls of arterioles as changes in blood flow occur through the vessel. This may be viewed as a largely protective function against dramatic fluctuations in blood pressure and blood flow to maintain homeostasis. If perfusion of an organ is too low (ischemia), the tissue will experience low levels of oxygen (hypoxia). In contrast, excessive perfusion could damage the organ's smaller and more fragile vessels. The myogenic response is a localized process that serves to stabilize blood flow in the capillary network that follows that arteriole.

When blood flow is low, the vessel's smooth muscle will be only minimally stretched. In response, it relaxes, allowing the vessel to dilate and thereby increase the movement of blood into the tissue. When blood flow is too high, the smooth muscle will contract in response to the increased stretch, prompting vasoconstriction that reduces blood flow.

Figure 20.20 summarizes the effects of nervous, endocrine, and local controls on arterioles.

exercise (see Figure 20.20). These changes result in selective vasodilation in the skeletal muscles, heart, lungs, liver, and integument. Simultaneously, vasoconstriction occurs in the vessels leading to the kidneys and most of the digestive and reproductive organs. The flow of blood to the brain remains largely unchanged whether at rest or exercising, since the vessels in the brain largely do not respond to regulatory stimuli, in most cases, because they lack the appropriate receptors.

As vasodilation occurs in selected vessels, resistance drops and more blood rushes into the organs they supply. This blood eventually returns to the venous system. Venous return is further enhanced by both the skeletal muscle and respiratory pumps. As blood returns to the heart more quickly, preload rises and the Frank-Starling principle tells us that contraction of the cardiac muscle in the atria and ventricles will be more forceful. Eventually, even the best-trained athletes will fatigue and must undergo a period of rest following exercise. Cardiac output and distribution of blood then return to normal.

Regular exercise promotes cardiovascular health in a variety of ways. Because an athlete's heart is larger than a nonathlete's, stroke volume increases, so the athletic heart can deliver the same amount of blood as the nonathletic heart but with a lower heart rate. This increased efficiency allows the athlete to exercise for longer periods of time before muscles fatigue and places less stress on the heart. Exercise also lowers overall cholesterol levels by removing from the circulation a complex form of cholesterol, triglycerides, and proteins known as low-density lipoproteins (LDLs), which are widely associated with increased risk of cardiovascular disease. Although there is no way to remove deposits of plaque from the walls of arteries other than specialized surgery, exercise does promote the health of vessels by decreasing the rate of plaque formation and reducing blood pressure, so the heart does not have to generate as much force to overcome resistance.

Generally as little as 30 minutes of noncontinuous exercise over the course of each day has beneficial effects and has been shown to lower the rate of heart attack by nearly 50 percent. While it is always advisable to follow a healthy diet, stop smoking, and lose weight, studies have clearly shown that fit, overweight people may actually be healthier overall than sedentary slender people. Thus, the benefits of moderate exercise are undeniable.

Clinical Considerations in Vascular Homeostasis

Any disorder that affects blood volume, vascular tone, or any other aspect of vascular functioning is likely to affect vascular homeostasis as well. That includes hypertension, hemorrhage, and shock.

Hypertension and Hypotension

New guidelines in 2017 from the American College of Cardiology and American Heart Association list normal blood pressure (BP) as less than 120/80 mm Hg and elevated BP as systolic P between 120–129 and diastolic P less than 80 mm Hg. Chronically elevated blood pressure is known clinically as **hypertension**. The new guidelines list hypertension that should be treated as 130/80 mm Hg. Tens of millions of Americans currently suffer from hypertension. Unfortunately, hypertension is typically a silent disorder; therefore, hypertensive patients may fail to recognize the seriousness of their condition and fail to follow their treatment plan. The result is often a heart attack or stroke. Hypertension may also lead to an aneurysm (ballooning of a blood vessel caused by a weakening of the wall), peripheral arterial disease (obstruction of vessels in peripheral regions of the body), chronic kidney disease, or heart failure.

INTERACTIVE LINK

Listen to this CDC podcast (http://openstax.org/l/CDCpodcast) to learn about hypertension, often described as a "silent killer." What steps can you take to reduce your risk of a heart attack or stroke?

Hemorrhage

Minor blood loss is managed by hemostasis and repair. Hemorrhage is a loss of blood that cannot be controlled by hemostatic mechanisms. Initially, the body responds to hemorrhage by initiating mechanisms aimed at increasing blood pressure and maintaining blood flow. Ultimately, however, blood volume will need to be restored, either through physiological processes or through medical intervention.

In response to blood loss, stimuli from the baroreceptors trigger the cardiovascular centers to stimulate sympathetic responses to increase cardiac output and vasoconstriction. This typically prompts the heart rate to

cardiogenic shock directly.

- **Vascular shock** occurs when arterioles lose their normal muscular tone and dilate dramatically. It may arise from a variety of causes, and treatments almost always involve fluid replacement and medications, called inotropic or pressor agents, which restore tone to the muscles of the vessels. In addition, eliminating or at least alleviating the underlying cause of the condition is required. This might include antibiotics and antihistamines, or select steroids, which may aid in the repair of nerve damage. A common cause is **sepsis** (or septicemia), also called "blood poisoning," which is a widespread bacterial infection that results in an organismal-level inflammatory response known as **septic shock**. **Neurogenic shock** is a form of vascular shock that occurs with cranial or spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region. **Anaphylactic shock** is a severe allergic response that causes the widespread release of histamines, triggering vasodilation throughout the body.
- **Obstructive shock**, as the name would suggest, occurs when a significant portion of the vascular system is blocked. It is not always recognized as a distinct condition and may be grouped with cardiogenic shock, including pulmonary embolism and cardiac tamponade. Treatments depend upon the underlying cause and, in addition to administering fluids intravenously, often include the administration of anticoagulants, removal of fluid from the pericardial cavity, or air from the thoracic cavity, and surgery as required. The most common cause is a pulmonary embolism, a clot that lodges in the pulmonary vessels and interrupts blood flow. Other causes include stenosis of the aortic valve; cardiac tamponade, in which excess fluid in the pericardial cavity interferes with the ability of the heart to fully relax and fill with blood (resulting in decreased preload); and a pneumothorax, in which an excessive amount of air is present in the thoracic cavity, outside of the lungs, which interferes with venous return, pulmonary function, and delivery of oxygen to the tissues.

20.5 Circulatory Pathways

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the vessels through which blood travels within the pulmonary circuit, beginning from the right ventricle of the heart and ending at the left atrium
- Create a flow chart showing the major systemic arteries through which blood travels from the aorta and its major branches, to the most significant arteries feeding into the right and left upper and lower limbs
- Create a flow chart showing the major systemic veins through which blood travels from the feet to the right atrium of the heart

Virtually every cell, tissue, organ, and system in the body is impacted by the circulatory system. This includes the generalized and more specialized functions of transport of materials, capillary exchange, maintaining health by transporting white blood cells and various immunoglobulins (antibodies), hemostasis, regulation of body temperature, and helping to maintain acid-base balance. In addition to these shared functions, many systems enjoy a unique relationship with the circulatory system. Figure 20.22 summarizes these relationships.

As you read about circular pathways, notice that there is an occasional, very large artery referred to as a **trunk**, a term indicating that the vessel gives rise to several smaller arteries. For example, the celiac trunk gives rise to the left gastric, common hepatic, and splenic arteries.

As you study this section, imagine you are on a "Voyage of Discovery" similar to Lewis and Clark's expedition in 1804–1806, which followed rivers and streams through unfamiliar territory, seeking a water route from the Atlantic to the Pacific Ocean. You might envision being inside a miniature boat, exploring the various branches of the circulatory system. This simple approach has proven effective for many students in mastering these major circulatory patterns. Another approach that works well for many students is to create simple line drawings similar to the ones provided, labeling each of the major vessels. It is beyond the scope of this text to name every vessel in the body. However, we will attempt to discuss the major pathways for blood and acquaint you with the major named arteries and veins in the body. Also, please keep in mind that individual variations in circulation patterns are not uncommon.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/arts1) for a brief summary of the arteries.

Pulmonary Circulation

Recall that blood returning from the systemic circuit enters the right atrium (Figure 20.23) via the superior and inferior venae cavae and the coronary sinus, which drains the blood supply of the heart muscle. These vessels will be described more fully later in this section. This blood is relatively low in oxygen and relatively high in carbon dioxide, since much of the oxygen has been extracted for use by the tissues and the waste gas carbon dioxide was picked up to be transported to the lungs for elimination. From the right atrium, blood moves into the right ventricle, which pumps it to the lungs for gas exchange. This system of vessels is referred to as the **pulmonary circuit**.

The single vessel exiting the right ventricle is the **pulmonary trunk**. At the base of the pulmonary trunk is the pulmonary semilunar valve, which prevents backflow of blood into the right ventricle during ventricular diastole. As the pulmonary trunk reaches the superior surface of the heart, it curves posteriorly and rapidly bifurcates (divides) into two branches, a left and a right **pulmonary artery**. To prevent confusion between these vessels, it is important to refer to the vessel exiting the heart as the pulmonary trunk, rather than also calling it a pulmonary artery. The pulmonary arteries in turn branch many times within the lung, forming a series of smaller arteries and arterioles that eventually lead to the pulmonary capillaries. The pulmonary capillaries surround lung structures known as alveoli that are the sites of oxygen and carbon dioxide exchange.

Once gas exchange is completed, oxygenated blood flows from the pulmonary capillaries into a series of pulmonary venules that eventually lead to a series of larger **pulmonary veins**. Four pulmonary veins, two on the left and two on the right, return blood to the left atrium. At this point, the pulmonary circuit is complete. Table 20.4 defines the major arteries and veins of the pulmonary circuit discussed in the text.

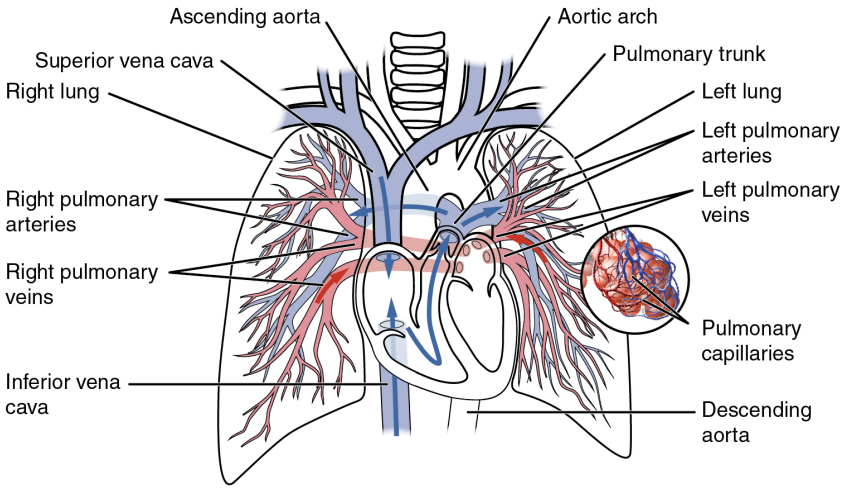


FIGURE 20.23 Pulmonary Circuit Blood exiting from the right ventricle flows into the pulmonary trunk, which bifurcates into the two

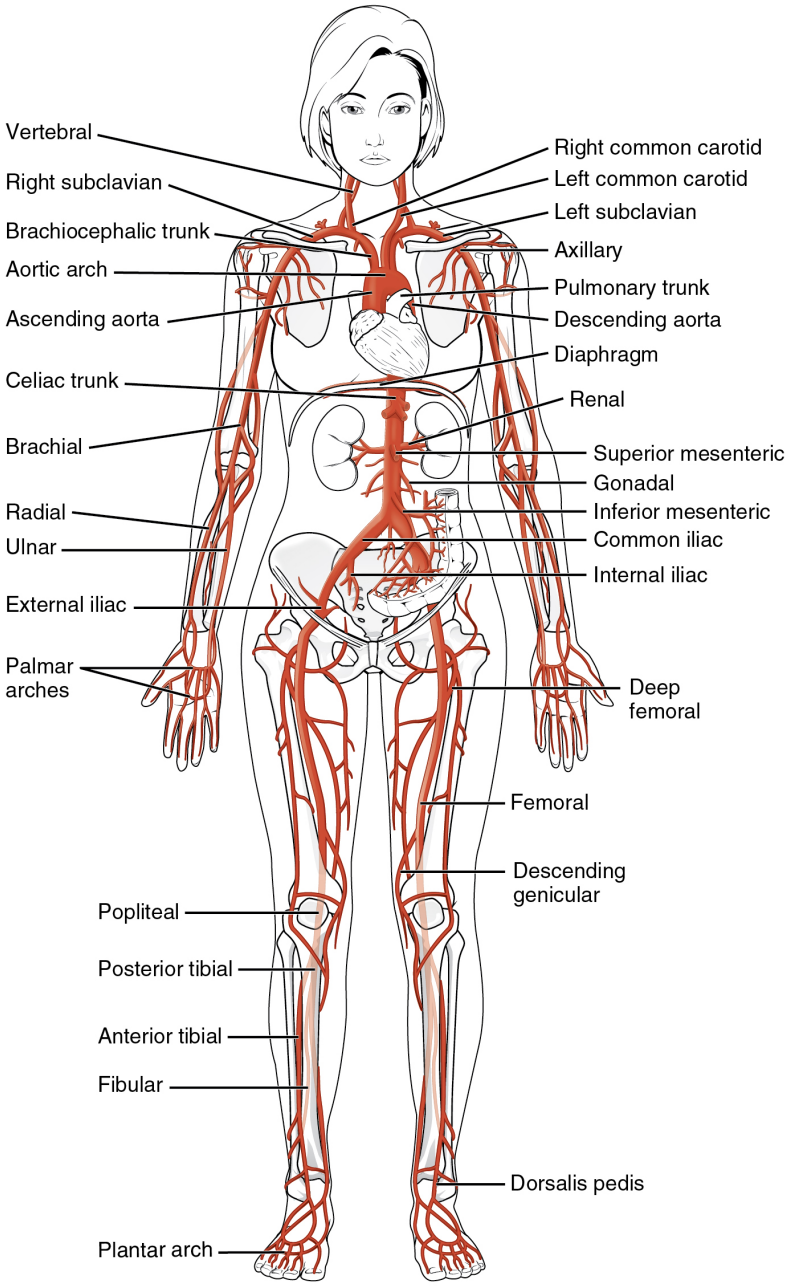


FIGURE 20.24 Systemic Arteries The major systemic arteries shown here deliver oxygenated blood throughout the body.

The Aorta

The **aorta** is the largest artery in the body (Figure 20.25). It arises from the left ventricle and eventually descends to the abdominal region, where it bifurcates at the level of the fourth lumbar vertebra into the two common iliac arteries. The aorta consists of the ascending aorta, the aortic arch, and the descending aorta, which passes through the diaphragm and a landmark that divides into the superior thoracic and inferior abdominal components. Arteries originating from the aorta ultimately distribute blood to virtually all tissues of the body. At the base of the aorta is the aortic semilunar valve that prevents backflow of blood into the left ventricle while the heart is relaxing. After exiting the heart, the **ascending aorta** moves in a superior direction for approximately 5 cm and ends at the sternal angle. Following this ascent, it reverses direction, forming a graceful arc to the left, called the **aortic arch**. The aortic arch descends toward the inferior portions of the body and ends at the level of the intervertebral disk between the fourth and fifth thoracic vertebrae. Beyond this point, the **descending aorta** continues close to the bodies of the vertebrae and passes through an opening in the diaphragm known as the **aortic hiatus**. Superior to the diaphragm, the aorta is called the **thoracic aorta**, and inferior to the diaphragm, it is called the **abdominal aorta**. The abdominal

Vessel	Description
Thoracic aorta	Portion of the descending aorta superior to the aortic hiatus
Abdominal aorta	Portion of the aorta inferior to the aortic hiatus and superior to the common iliac arteries

TABLE 20.5

Coronary Circulation

The first vessels that branch from the ascending aorta are the paired coronary arteries (see Figure 20.25), which arise from two of the three sinuses in the ascending aorta just superior to the aortic semilunar valve. These sinuses contain the aortic baroreceptors and chemoreceptors critical to maintain cardiac function. The left coronary artery arises from the left posterior aortic sinus. The right coronary artery arises from the anterior aortic sinus. Normally, the right posterior aortic sinus does not give rise to a vessel.

The coronary arteries encircle the heart, forming a ring-like structure that divides into the next level of branches that supplies blood to the heart tissues. (Seek additional content for more detail on cardiac circulation.)

Aortic Arch Branches

There are three major branches of the aortic arch: the brachiocephalic artery, the left common carotid artery, and the left subclavian (literally “under the clavicle”) artery. As you would expect based upon proximity to the heart, each of these vessels is classified as an elastic artery.

The brachiocephalic artery is located only on the right side of the body; there is no corresponding artery on the left. The brachiocephalic artery branches into the right subclavian artery and the right common carotid artery. The left subclavian and left common carotid arteries arise independently from the aortic arch but otherwise follow a similar pattern and distribution to the corresponding arteries on the right side (see Figure 20.23).

Each **subclavian artery** supplies blood to the arms, chest, shoulders, back, and central nervous system. It then gives rise to three major branches: the internal thoracic artery, the vertebral artery, and the thyrocervical artery. The **internal thoracic artery**, or mammary artery, supplies blood to the thymus, the pericardium of the heart, and the anterior chest wall. The **vertebral artery** passes through the vertebral foramen in the cervical vertebrae and then through the foramen magnum into the cranial cavity to supply blood to the brain and spinal cord. The paired vertebral arteries join together to form the large basilar artery at the base of the medulla oblongata. This is an example of an anastomosis. The subclavian artery also gives rise to the **thyrocervical artery** that provides blood to the thyroid, the cervical region of the neck, and the upper back and shoulder.

The **common carotid artery** divides into internal and external carotid arteries. The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises directly from the aortic arch. The **external carotid artery** supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx. These branches include the lingual, facial, occipital, maxillary, and superficial temporal arteries. The **internal carotid artery** initially forms an expansion known as the carotid sinus, containing the carotid baroreceptors and chemoreceptors. Like their counterparts in the aortic sinuses, the information provided by these receptors is critical to maintaining cardiovascular homeostasis (see Figure 20.23).

The internal carotid arteries along with the vertebral arteries are the two primary suppliers of blood to the human brain. Given the central role and vital importance of the brain to life, it is critical that blood supply to this organ remains uninterrupted. Recall that blood flow to the brain is remarkably constant, with approximately 20 percent of blood flow directed to this organ at any given time. When blood flow is interrupted, even for just a few seconds, a **transient ischemic attack (TIA)**, or mini-stroke, may occur, resulting in loss of consciousness or temporary loss of neurological function. In some cases, the damage may be permanent. Loss of blood flow for longer periods, typically between 3 and 4 minutes, will likely produce irreversible brain damage or a stroke, also called a **cerebrovascular accident (CVA)**. The locations of the arteries in the brain not only provide blood flow to the brain tissue but also prevent interruption in the flow of blood. Both the carotid and vertebral arteries branch once they enter the cranial

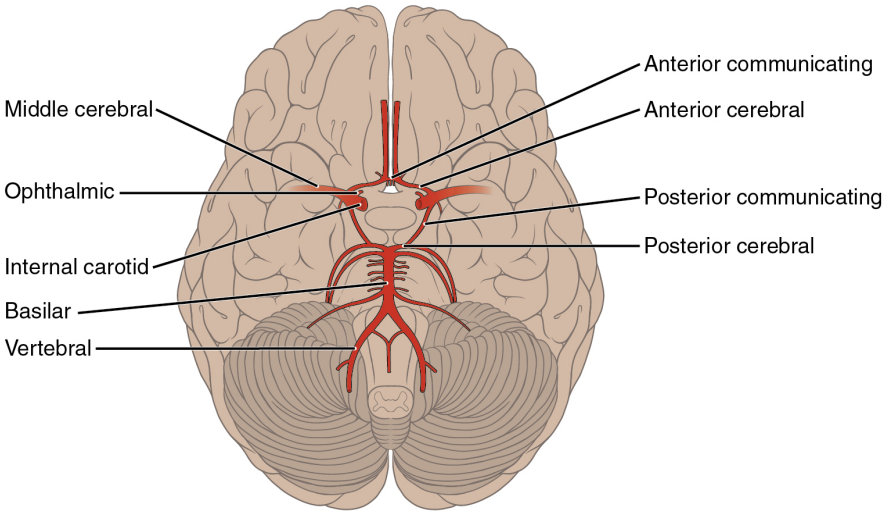


FIGURE 20.27 Arteries Serving the Brain This inferior view shows the network of arteries serving the brain. The structure is referred to as the arterial circle or circle of Willis.

Aortic Arch Branches and Brain Circulation

Vessel	Description
Brachiocephalic artery	Single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region
Subclavian artery	The right subclavian artery arises from the brachiocephalic artery while the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system
Internal thoracic artery	Also called the mammary artery; arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and anterior chest wall
Vertebral artery	Arises from the subclavian artery and passes through the vertebral foramen through the foramen magnum to the brain; joins with the internal carotid artery to form the arterial circle; supplies blood to the brain and spinal cord
Thyrocervical artery	Arises from the subclavian artery; supplies blood to the thyroid, the cervical region, the upper back, and shoulder
Common carotid artery	The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises from the aortic arch; each gives rise to the external and internal carotid arteries; supplies the respective sides of the head and neck
External carotid artery	Arises from the common carotid artery; supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx

TABLE 20.6

diaphragm. Table 20.7 lists the arteries of the thoracic region.

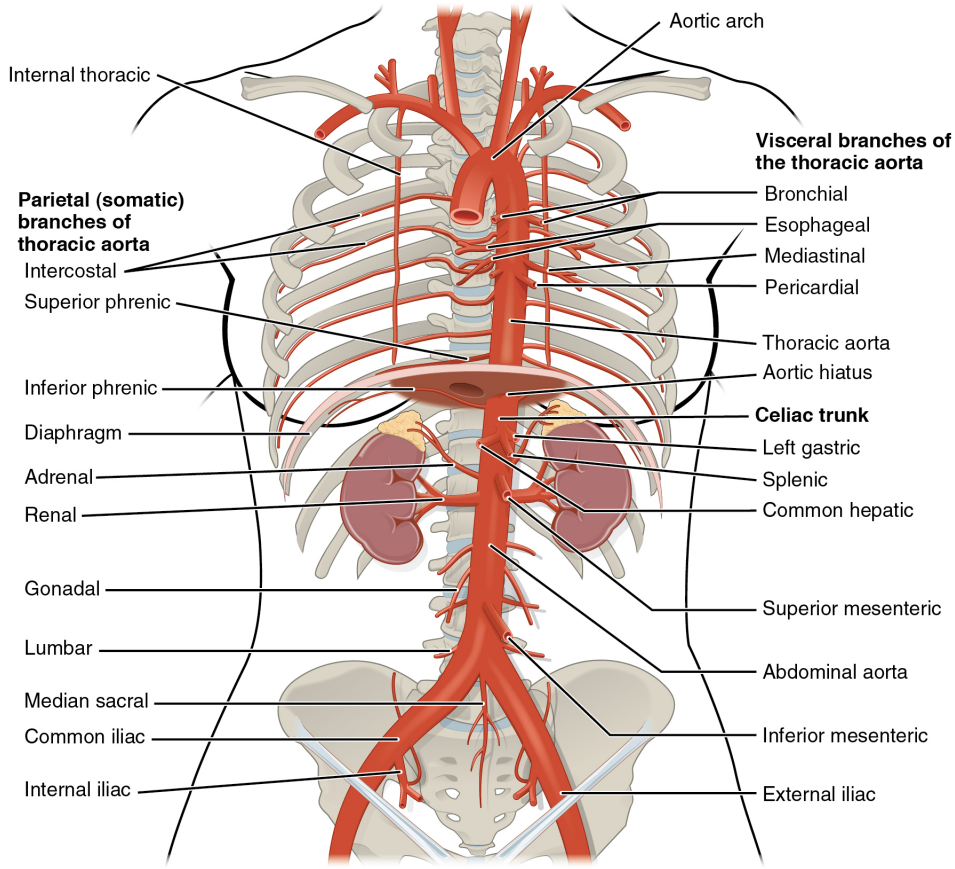


FIGURE 20.28 Arteries of the Thoracic and Abdominal Regions The thoracic aorta gives rise to the arteries of the visceral and parietal branches.

Arteries of the Thoracic Region

Vessel	Description
Visceral branches	A group of arterial branches of the thoracic aorta; supplies blood to the viscera (i.e., organs) of the thorax
Bronchial artery	Systemic branch from the aorta that provides oxygenated blood to the lungs; this blood supply is in addition to the pulmonary circuit that brings blood for oxygenation
Pericardial artery	Branch of the thoracic aorta; supplies blood to the pericardium
Esophageal artery	Branch of the thoracic aorta; supplies blood to the esophagus
Mediastinal artery	Branch of the thoracic aorta; supplies blood to the mediastinum

TABLE 20.7

uterus and vagina. The much larger **external iliac artery** supplies blood to each of the lower limbs. Figure 20.29 shows the distribution of the major branches of the aorta into the thoracic and abdominal regions. Figure 20.30 shows the distribution of the major branches of the common iliac arteries. Table 20.8 summarizes the major branches of the abdominal aorta.

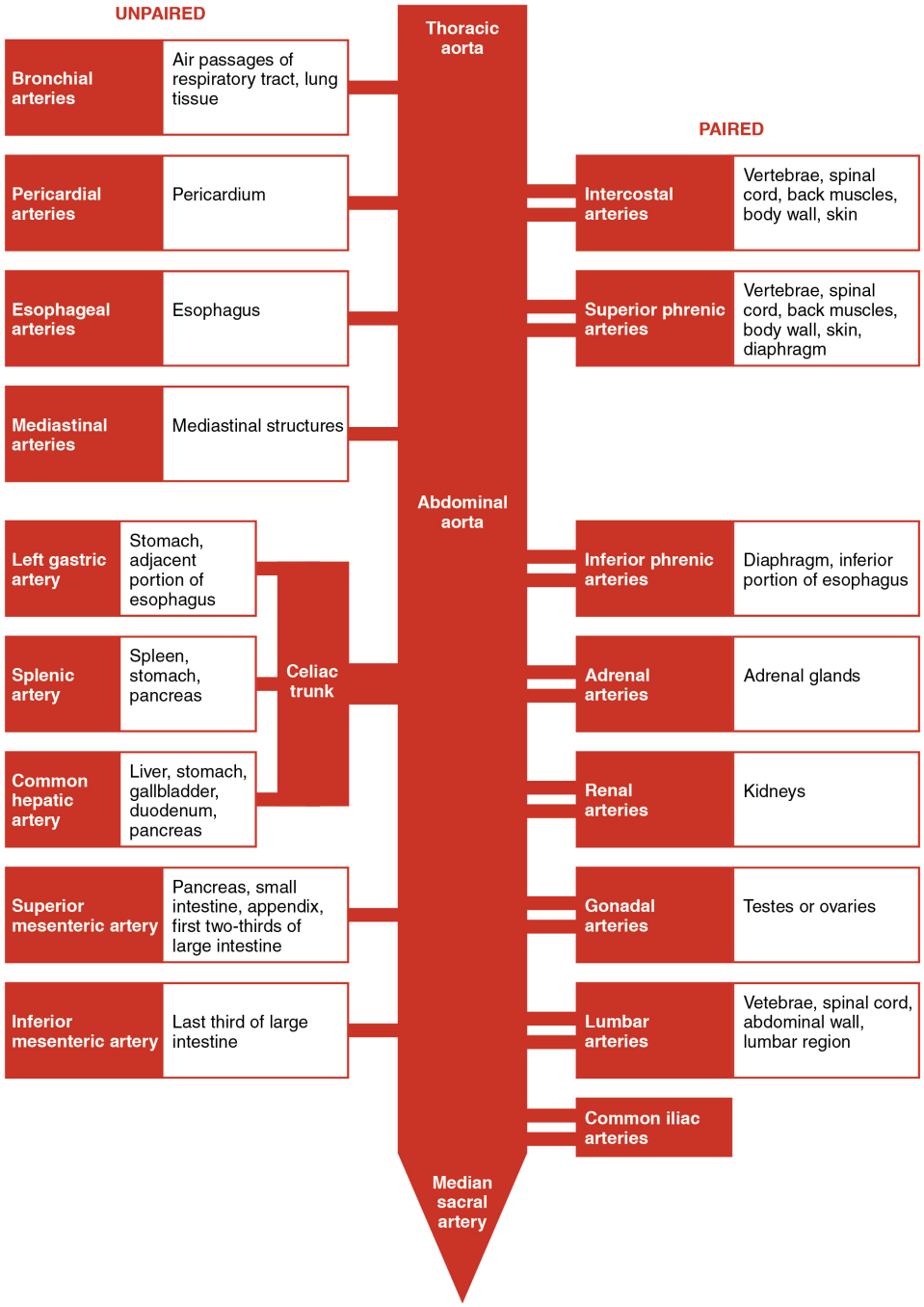


FIGURE 20.29 Major Branches of the Aorta The flow chart summarizes the distribution of the major branches of the aorta into the thoracic and abdominal regions.

Vessel	Description
Cystic artery	Branch of the common hepatic artery; supplies blood to the gall bladder
Superior mesenteric artery	Branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine
Inferior mesenteric artery	Branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum
Inferior phrenic arteries	Branches of the abdominal aorta; supply blood to the inferior surface of the diaphragm
Adrenal artery	Branch of the abdominal aorta; supplies blood to the adrenal (suprarenal) glands
Renal artery	Branch of the abdominal aorta; supplies each kidney
Gonadal artery	Branch of the abdominal aorta; supplies blood to the gonads or reproductive organs; also described as ovarian arteries or testicular arteries, depending upon the sex of the individual
Ovarian artery	Branch of the abdominal aorta; supplies blood to ovary, uterine (Fallopian) tube, and uterus
Testicular artery	Branch of the abdominal aorta; ultimately travels outside the body cavity to the testes and forms one component of the spermatic cord
Lumbar arteries	Branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord
Common iliac artery	Branch of the aorta that leads to the internal and external iliac arteries
Median sacral artery	Continuation of the aorta into the sacrum
Internal iliac artery	Branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provides blood to the uterus and vagina
External iliac artery	Branch of the common iliac artery that leaves the body cavity and becomes a femoral artery; supplies blood to the lower limbs

TABLE 20.8

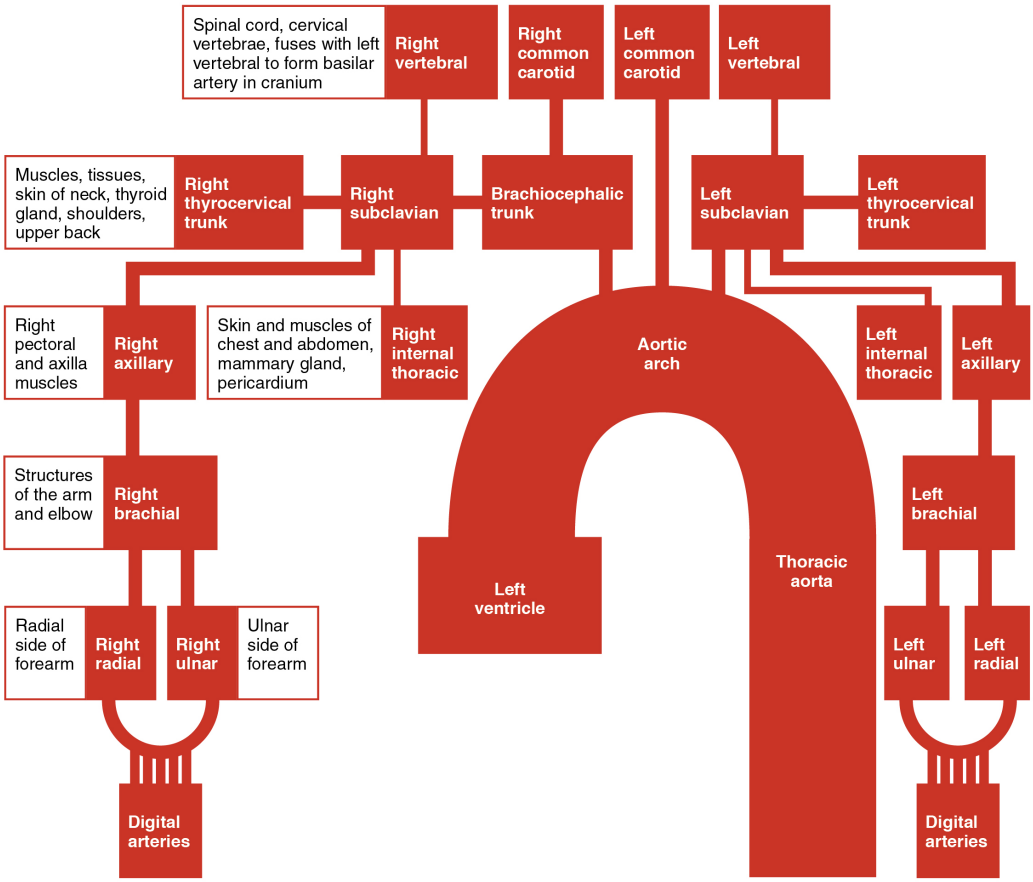


FIGURE 20.32 **Major Arteries of the Upper Limb** The flow chart summarizes the distribution of the major arteries from the heart into the upper limb.

Arteries Serving the Upper Limbs

Vessel	Description
Axillary artery	Continuation of the subclavian artery as it penetrates the body wall and enters the axillary region; supplies blood to the region near the head of the humerus (humeral circumflex arteries); the majority of the vessel continues into the brachium and becomes the brachial artery
Brachial artery	Continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa
Radial artery	Formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region
Ulnar artery	Formed at the bifurcation of the brachial artery; parallels the ulna; gives off smaller branches until it reaches the carpal region where it fuses with the radial artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

TABLE 20.9

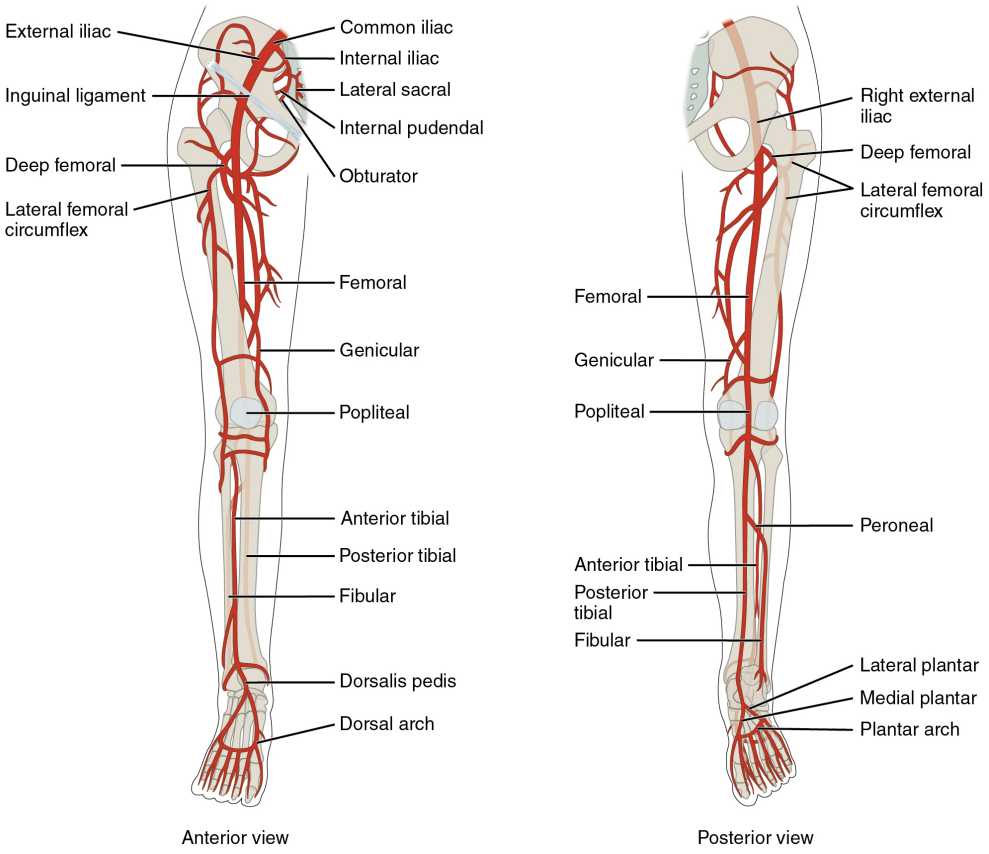


FIGURE 20.33 Major Arteries Serving the Lower Limb Major arteries serving the lower limb are shown in anterior and posterior views.

Vessel	Description
Genicular artery	Branch of the femoral artery; supplies blood to the region of the knee
Popliteal artery	Continuation of the femoral artery posterior to the knee; branches into the anterior and posterior tibial arteries
Anterior tibial artery	Branches from the popliteal artery; supplies blood to the anterior tibial region; becomes the dorsalis pedis artery
Dorsalis pedis artery	Forms from the anterior tibial artery; branches repeatedly to supply blood to the tarsal and dorsal regions of the foot
Posterior tibial artery	Branches from the popliteal artery and gives rise to the fibular or peroneal artery; supplies blood to the posterior tibial region
Medial plantar artery	Arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot
Lateral plantar artery	Arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot
Dorsal or arcuate arch	Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits
Plantar arch	Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits

TABLE 20.10

Overview of Systemic Veins

Systemic veins return blood to the right atrium. Since the blood has already passed through the systemic capillaries, it will be relatively low in oxygen concentration. In many cases, there will be veins draining organs and regions of the body with the same name as the arteries that supplied these regions and the two often parallel one another. This is often described as a "complementary" pattern. However, there is a great deal more variability in the venous circulation than normally occurs in the arteries. For the sake of brevity and clarity, this text will discuss only the most commonly encountered patterns. However, keep this variation in mind when you move from the classroom to clinical practice.

In both the neck and limb regions, there are often both superficial and deeper levels of veins. The deeper veins generally correspond to the complementary arteries. The superficial veins do not normally have direct arterial counterparts, but in addition to returning blood, they also make contributions to the maintenance of body temperature. When the ambient temperature is warm, more blood is diverted to the superficial veins where heat can be more easily dissipated to the environment. In colder weather, there is more constriction of the superficial veins and blood is diverted deeper where the body can retain more of the heat.

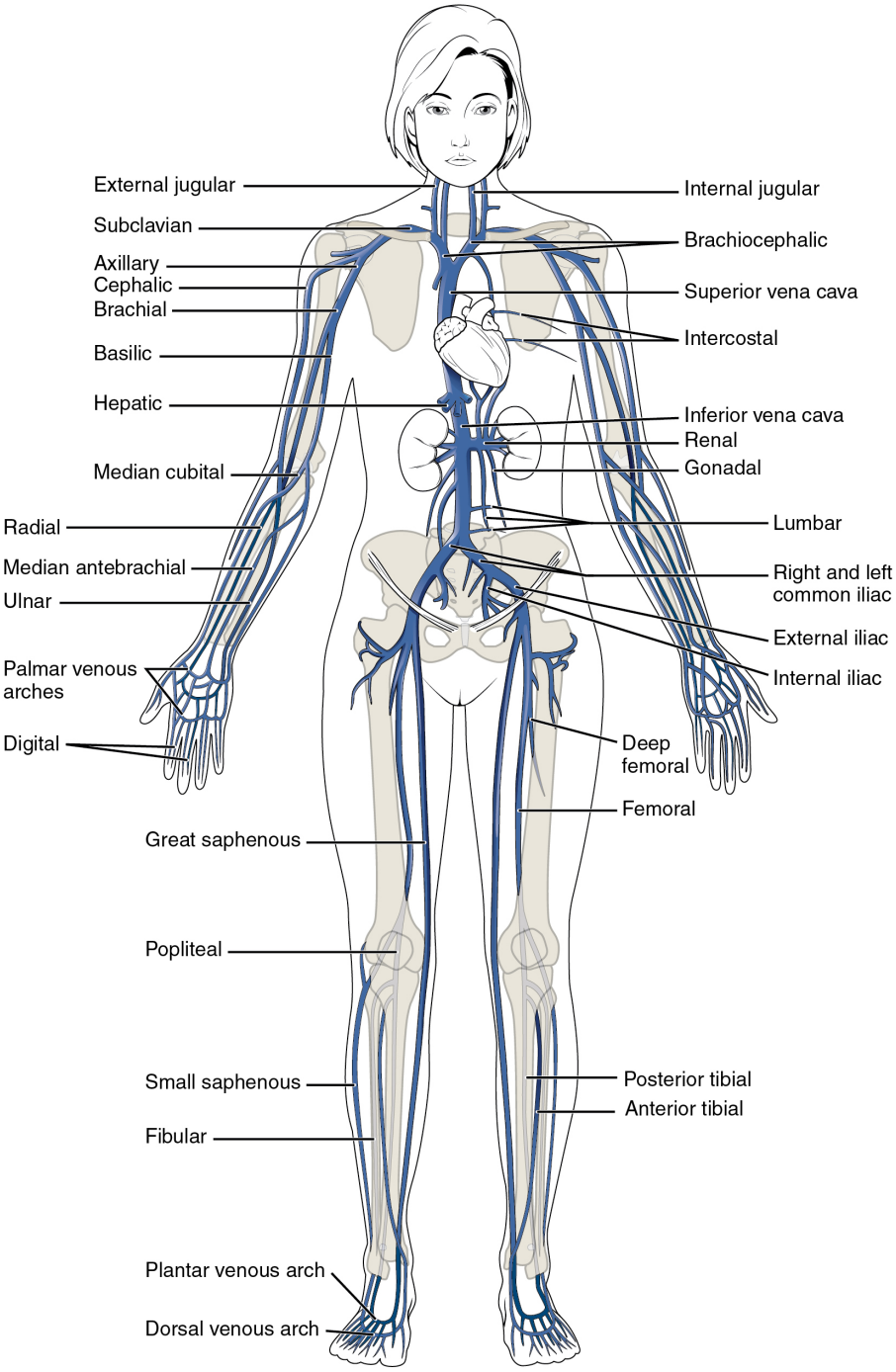


FIGURE 20.35 Major Systemic Veins of the Body The major systemic veins of the body are shown here in an anterior view.

The right atrium receives all of the systemic venous return. Most of the blood flows into either the superior vena cava or inferior vena cava. If you draw an imaginary line at the level of the diaphragm, systemic venous circulation from above that line will generally flow into the superior vena cava; this includes blood from the head, neck, chest, shoulders, and upper limbs. The exception to this is that most venous blood flow from the coronary veins flows directly into the coronary sinus and from there directly into the right atrium. Beneath the diaphragm, systemic venous flow enters the inferior vena cava, that is, blood from the abdominal and pelvic regions and the lower limbs.

The Superior Vena Cava

The **superior vena cava** drains most of the body superior to the diaphragm (Figure 20.36). On both the left and right sides, the **subclavian vein** forms when the axillary vein passes through the body wall from the axillary region. It fuses with the external and internal jugular veins from the head and neck to form the **brachiocephalic vein**. Each

Veins of the Thoracic Region

Vessel	Description
Superior vena cava	Large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium
Subclavian vein	Located deep in the thoracic cavity; formed by the axillary vein as it enters the thoracic cavity from the axillary region; drains the axillary and smaller local veins near the scapular region and leads to the brachiocephalic vein
Brachiocephalic veins	Pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins flow into it; drain the upper thoracic region and lead to the superior vena cava
Vertebral vein	Arises from the base of the brain and the cervical region of the spinal cord; passes through the intervertebral foramina in the cervical vertebrae; drains smaller veins from the cranium, spinal cord, and vertebrae, and leads to the brachiocephalic vein; counterpart of the vertebral artery
Internal thoracic veins	Also called internal mammary veins; drain the anterior surface of the chest wall and lead to the brachiocephalic vein
Intercostal vein	Drains the muscles of the thoracic wall and leads to the azygos vein
Esophageal vein	Drains the inferior portions of the esophagus and leads to the azygos vein
Bronchial vein	Drains the systemic circulation from the lungs and leads to the azygos vein
Azygos vein	Originates in the lumbar region and passes through the diaphragm into the thoracic cavity on the right side of the vertebral column; drains blood from the intercostal veins, esophageal veins, bronchial veins, and other veins draining the mediastinal region, and leads to the superior vena cava
Hemiazygos vein	Smaller vein complementary to the azygos vein; drains the esophageal veins from the esophagus and the left intercostal veins, and leads to the brachiocephalic vein via the superior intercostal vein

TABLE 20.11

Veins of the Head and Neck

Blood from the brain and the superficial facial vein flow into each **internal jugular vein** (Figure 20.37). Blood from the more superficial portions of the head, scalp, and cranial regions, including the **temporal vein** and **maxillary vein**, flow into each **external jugular vein**. Although the external and internal jugular veins are separate vessels, there are anastomoses between them close to the thoracic region. Blood from the external jugular vein empties into the subclavian vein. Table 20.12 summarizes the major veins of the head and neck.

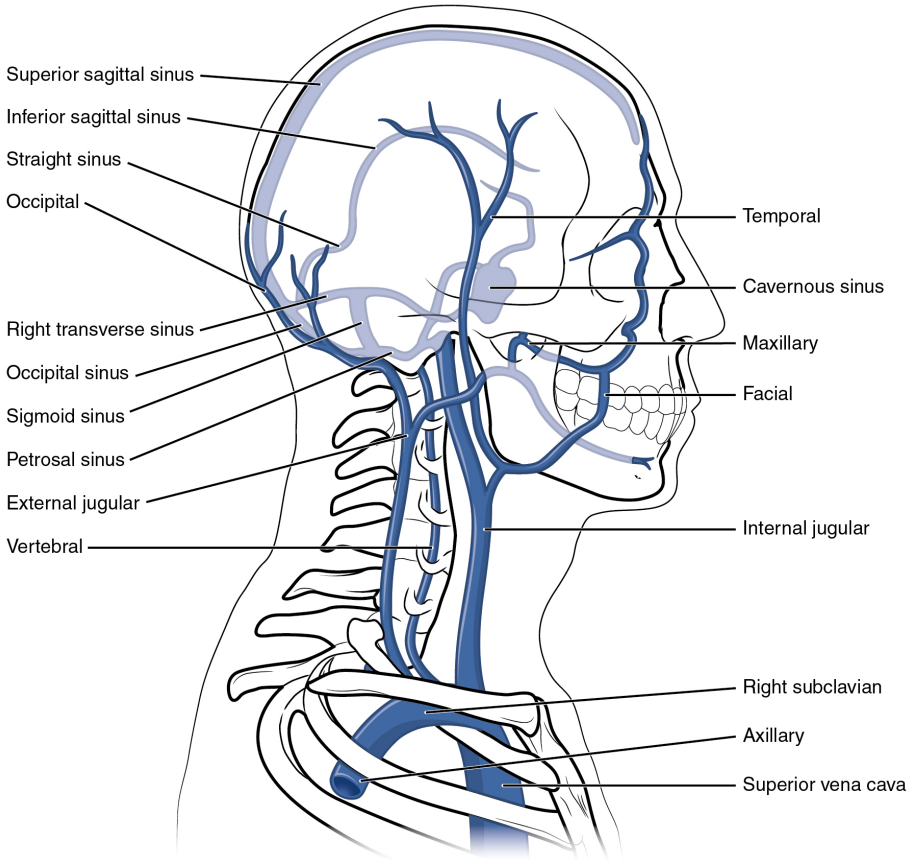


FIGURE 20.37 **Veins of the Head and Neck** This left lateral view shows the veins of the head and neck, including the intercranial sinuses.

Major Veins of the Brain

Vessel	Description
Superior sagittal sinus	Enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein
Great cerebral vein	Receives most of the smaller vessels from the inferior cerebral veins and leads to the straight sinus
Straight sinus	Enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and leads to the left or right transverse sinus
Cavernous sinus	Enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus
Petrosal sinus	Enlarged vein that receives blood from the cavernous sinus and leads into the internal jugular veins

TABLE 20.13

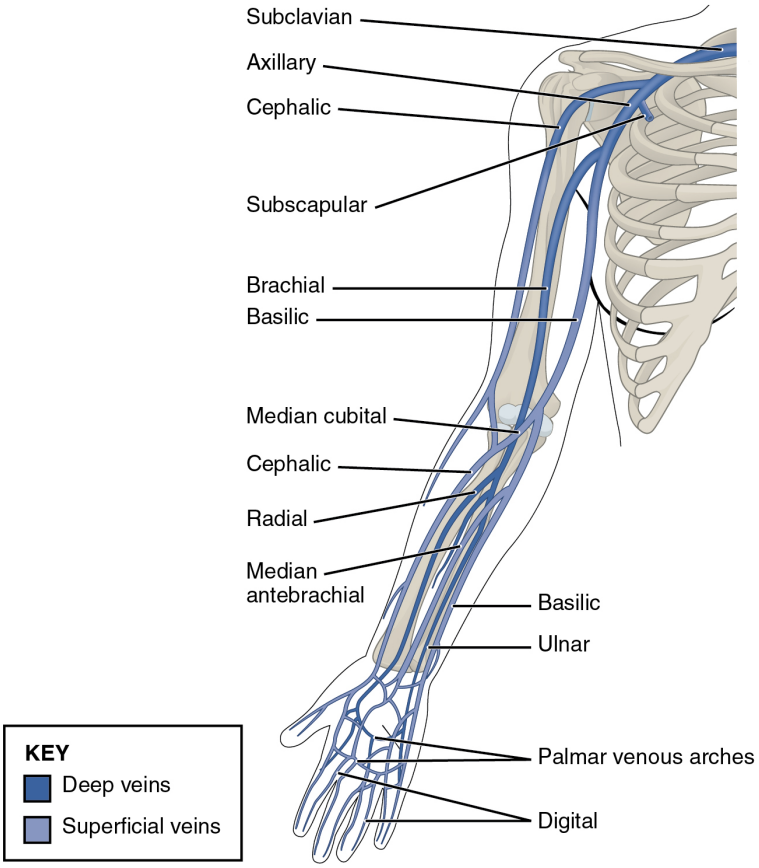


FIGURE 20.38 Veins of the Upper Limb This anterior view shows the veins that drain the upper limb.

Vessel	Description
Brachial vein	Deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein
Median antebrachial vein	Vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches; leads to the basilic vein
Basilic vein	Superficial vein of the arm that arises from the median antebrachial vein, intersects with the median cubital vein, parallels the ulnar vein, and continues into the upper arm; along with the brachial vein, it leads to the axillary vein
Median cubital vein	Superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site from which to draw blood
Cephalic vein	Superficial vessel in the upper arm; leads to the axillary vein
Subscapular vein	Drains blood from the subscapular region and leads to the axillary vein
Axillary vein	The major vein in the axillary region; drains the upper limb and becomes the subclavian vein

TABLE 20.14

The Inferior Vena Cava

Other than the small amount of blood drained by the azygos and hemiazygos veins, most of the blood inferior to the diaphragm drains into the inferior vena cava before it is returned to the heart (see Figure 20.36). Lying just beneath the parietal peritoneum in the abdominal cavity, the **inferior vena cava** parallels the abdominal aorta, where it can receive blood from abdominal veins. The lumbar portions of the abdominal wall and spinal cord are drained by a series of **lumbar veins**, usually four on each side. The ascending lumbar veins drain into either the azygos vein on the right or the hemiazygos vein on the left, and return to the superior vena cava. The remaining lumbar veins drain directly into the inferior vena cava.

Blood supply from the kidneys flows into each **renal vein**, normally the largest veins entering the inferior vena cava. A number of other, smaller veins empty into the left renal vein. Each **adrenal vein** drains the adrenal or suprarenal glands located immediately superior to the kidneys. The right adrenal vein enters the inferior vena cava directly, whereas the left adrenal vein enters the left renal vein.

From the male reproductive organs, each **testicular vein** flows from the scrotum, forming a portion of the spermatic cord. Each **ovarian vein** drains an ovary in females. Each of these veins is generically called a **gonadal vein**. The right gonadal vein empties directly into the inferior vena cava, and the left gonadal vein empties into the left renal vein.

Each side of the diaphragm drains into a **phrenic vein**; the right phrenic vein empties directly into the inferior vena cava, whereas the left phrenic vein empties into the left renal vein. Blood supply from the liver drains into each **hepatic vein** and directly into the inferior vena cava. Since the inferior vena cava lies primarily to the right of the vertebral column and aorta, the left renal vein is longer, as are the left phrenic, adrenal, and gonadal veins. The longer length of the left renal vein makes the left kidney the primary target of surgeons removing this organ for donation. Figure 20.40 provides a flow chart of the veins flowing into the inferior vena cava. Table 20.15 summarizes the major veins of the abdominal region.

Vessel	Description
Adrenal vein	Drains the adrenal or suprarenal; the right adrenal vein enters the inferior vena cava directly and the left adrenal vein enters the left renal vein
Testicular vein	Drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein
Ovarian vein	Drains the ovary; the right ovarian vein empties directly into the inferior vena cava and the left ovarian vein empties into the left renal vein
Gonadal vein	Generic term for a vein draining a reproductive organ; may be either an ovarian vein or a testicular vein, depending on the sex of the individual
Phrenic vein	Drains the diaphragm; the right phrenic vein flows into the inferior vena cava and the left phrenic vein empties into the left renal vein
Hepatic vein	Drains systemic blood from the liver and flows into the inferior vena cava

TABLE 20.15

Veins Draining the Lower Limbs

The superior surface of the foot drains into the digital veins, and the inferior surface drains into the **plantar veins**, which flow into a complex series of anastomoses in the feet and ankles, including the **dorsal venous arch** and the **plantar venous arch** (Figure 20.41). From the dorsal venous arch, blood supply drains into the anterior and posterior tibial veins. The **anterior tibial vein** drains the area near the tibialis anterior muscle and combines with the posterior tibial vein and the fibular vein to form the popliteal vein. The **posterior tibial vein** drains the posterior surface of the tibia and joins the popliteal vein. The **fibular vein** drains the muscles and integument in proximity to the fibula and also joins the popliteal vein. The **small saphenous vein** located on the lateral surface of the leg drains blood from the superficial regions of the lower leg and foot, and flows into to the **popliteal vein**. As the popliteal vein passes behind the knee in the popliteal region, it becomes the femoral vein. It is palpable in patients without excessive adipose tissue.

Close to the body wall, the great saphenous vein, the deep femoral vein, and the femoral circumflex vein drain into the femoral vein. The **great saphenous vein** is a prominent surface vessel located on the medial surface of the leg and thigh that collects blood from the superficial portions of these areas. The **deep femoral vein**, as the name suggests, drains blood from the deeper portions of the thigh. The **femoral circumflex vein** forms a loop around the femur just inferior to the trochanters and drains blood from the areas in proximity to the head and neck of the femur.

As the **femoral vein** penetrates the body wall from the femoral portion of the upper limb, it becomes the **external iliac vein**, a large vein that drains blood from the leg to the common iliac vein. The pelvic organs and integument drain into the **internal iliac vein**, which forms from several smaller veins in the region, including the umbilical veins that run on either side of the bladder. The external and internal iliac veins combine near the inferior portion of the sacroiliac joint to form the common iliac vein. In addition to blood supply from the external and internal iliac veins, the **middle sacral vein** drains the sacral region into the **common iliac vein**. Similar to the common iliac arteries, the common iliac veins come together at the level of L5 to form the inferior vena cava.

Figure 20.42 is a flow chart of veins flowing into the lower limb. Table 20.16 summarizes the major veins of the lower limbs.

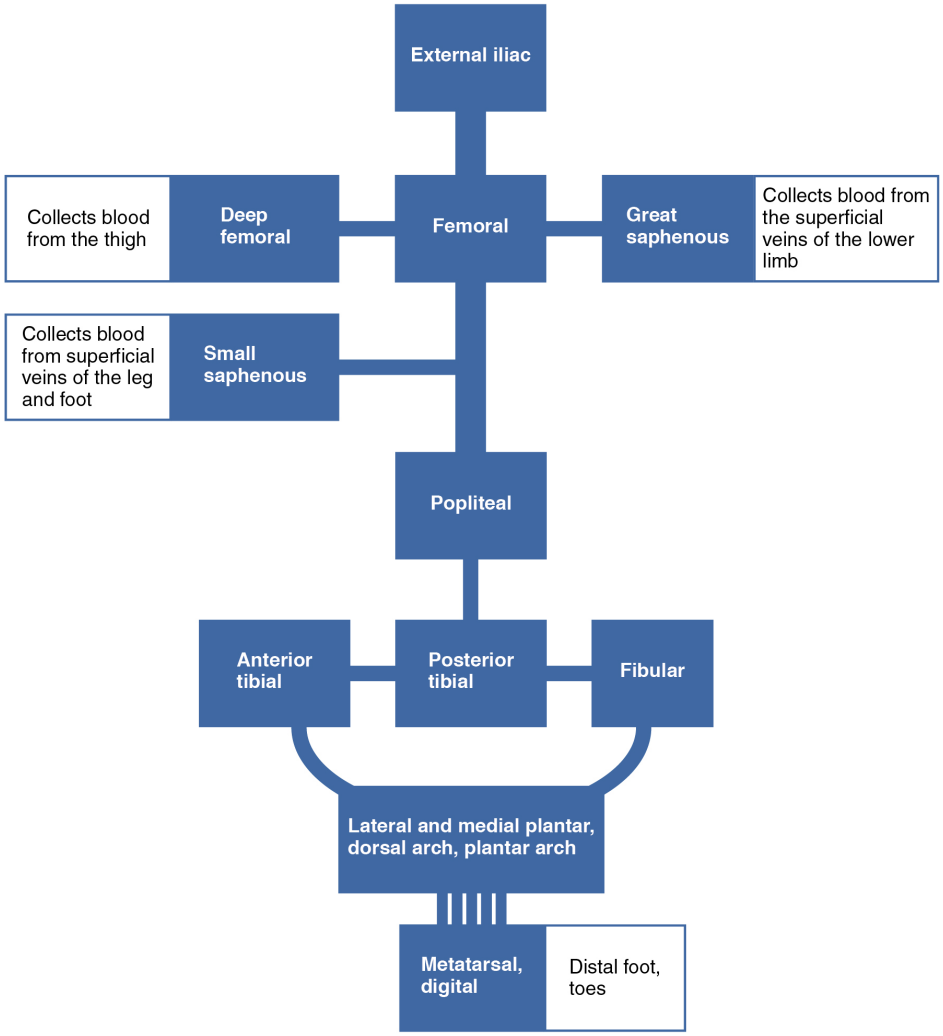


FIGURE 20.42 **Major Veins of the Lower Limb** The flow chart summarizes venous flow from the lower limb.

Veins of the Lower Limbs

Vessel	Description
Plantar veins	Drain the foot and flow into the plantar venous arch
Dorsal venous arch	Drains blood from digital veins and vessels on the superior surface of the foot
Plantar venous arch	Formed from the plantar veins; flows into the anterior and posterior tibial veins through anastomoses
Anterior tibial vein	Formed from the dorsal venous arch; drains the area near the tibialis anterior muscle and flows into the popliteal vein

TABLE 20.16

sinusoids. You saw the only other portal system with the hypothalamic-hypophyseal portal vessel in the endocrine chapter.

The hepatic portal system consists of the hepatic portal vein and the veins that drain into it. The hepatic portal vein itself is relatively short, beginning at the level of L2 with the confluence of the superior mesenteric and splenic veins. It also receives branches from the inferior mesenteric vein, plus the splenic veins and all their tributaries. The superior mesenteric vein receives blood from the small intestine, two-thirds of the large intestine, and the stomach. The inferior mesenteric vein drains the distal third of the large intestine, including the descending colon, the sigmoid colon, and the rectum. The splenic vein is formed from branches from the spleen, pancreas, and portions of the stomach, and the inferior mesenteric vein. After its formation, the hepatic portal vein also receives branches from the gastric veins of the stomach and cystic veins from the gall bladder. The hepatic portal vein delivers materials from these digestive and circulatory organs directly to the liver for processing.

Because of the hepatic portal system, the liver receives its blood supply from two different sources: from normal systemic circulation via the hepatic artery and from the hepatic portal vein. The liver processes the blood from the portal system to remove certain wastes and excess nutrients, which are stored for later use. This processed blood, as well as the systemic blood that came from the hepatic artery, exits the liver via the right, left, and middle hepatic veins, and flows into the inferior vena cava. Overall systemic blood composition remains relatively stable, since the liver is able to metabolize the absorbed digestive components.

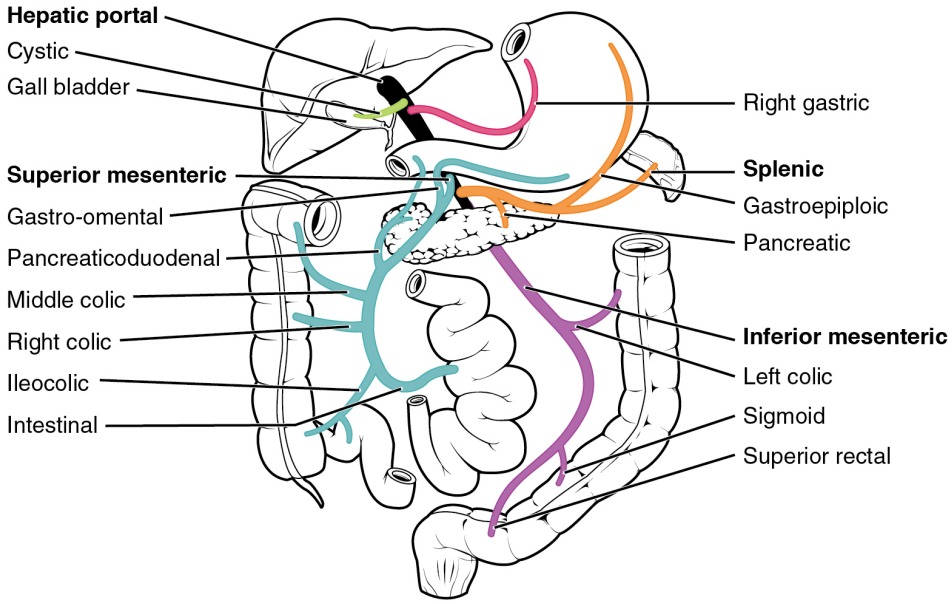


FIGURE 20.43 Hepatic Portal System The liver receives blood from the normal systemic circulation via the hepatic artery. It also receives and processes blood from other organs, delivered via the veins of the hepatic portal system. All blood exits the liver via the hepatic vein, which delivers the blood to the inferior vena cava. (Different colors are used to help distinguish among the different vessels in the system.)

20.6 Development of Blood Vessels and Fetal Circulation

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the development of blood vessels
- Describe the fetal circulation

In a developing embryo,the heart has developed enough by day 21 post-fertilization to begin beating. Circulation patterns are clearly established by the fourth week of embryonic life. It is critical to the survival of the developing human that the circulatory system forms early to supply the growing tissue with nutrients and gases, and to remove waste products. Blood cells and vessel production in structures outside the embryo proper called the yolk sac, chorion, and connecting stalk begin about 15 to 16 days following fertilization. Development of these circulatory elements within the embryo itself begins approximately 2 days later. You will learn more about the formation and

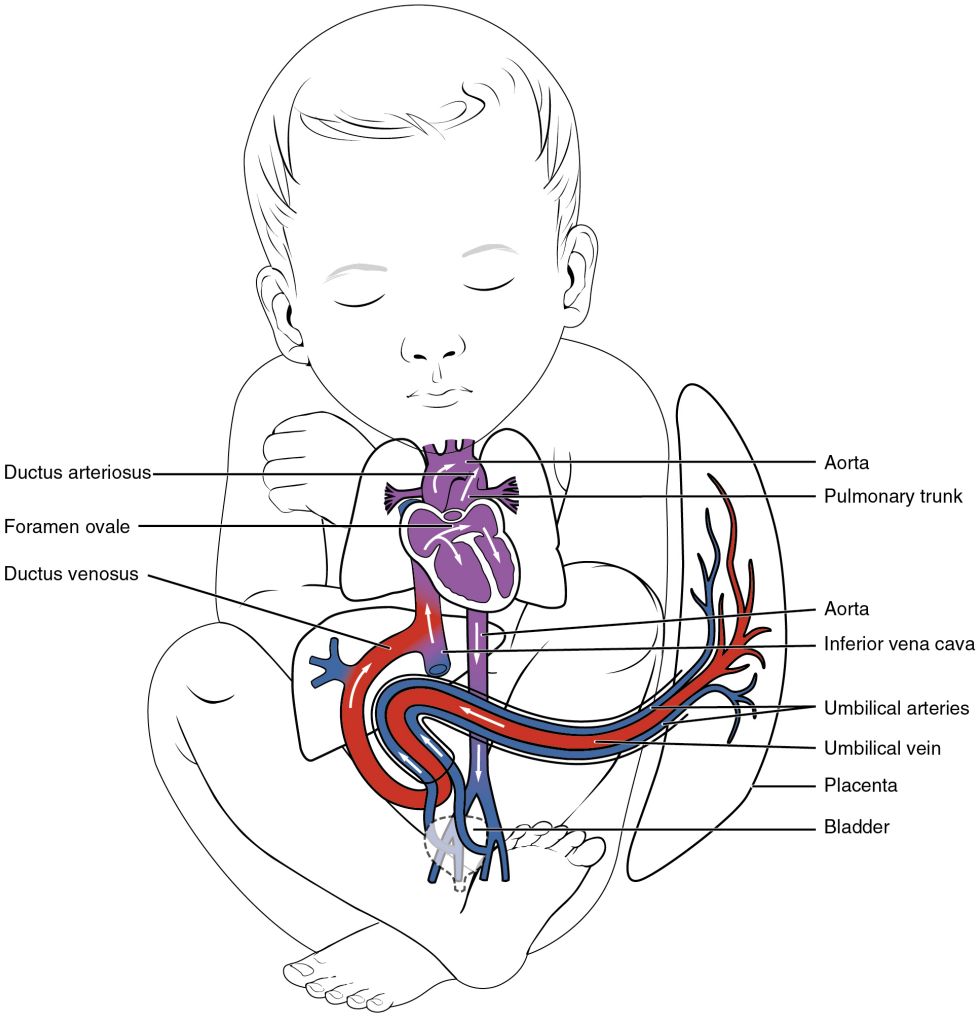


FIGURE 20.44 Fetal Shunts The foramen ovale in the interatrial septum allows blood to flow from the right atrium to the left atrium. The ductus arteriosus is a temporary vessel, connecting the aorta to the pulmonary trunk. The ductus venosus links the umbilical vein to the inferior vena cava largely through the liver.

the wall of a vessel or heart chamber; can be described with the more generic term hydrostatic pressure

brachial artery continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa

brachial vein deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein

brachiocephalic artery single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region

brachiocephalic vein one of a pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins lead to it; drains the upper thoracic region and flows into the superior vena cava

bronchial artery systemic branch from the aorta that provides oxygenated blood to the lungs in addition to the pulmonary circuit

bronchial vein drains the systemic circulation from the lungs and leads to the azygos vein

capacitance ability of a vein to distend and store blood

capacitance vessels veins

capillary smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed network of 10–100 capillaries connecting arterioles to venules

capillary hydrostatic pressure (CHP) force blood exerts against a capillary

cardiogenic shock type of shock that results from the inability of the heart to maintain cardiac output

carotid sinuses small pockets near the base of the internal carotid arteries that are the locations of the baroreceptors and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

cavernous sinus enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus

celiac trunk (also, celiac artery) major branch of the abdominal aorta; gives rise to the left gastric artery, the splenic artery, and the common hepatic artery that forms the hepatic artery to the liver, the right gastric artery to the stomach, and the cystic artery to the gall bladder

cephalic vein superficial vessel in the upper arm; leads to the axillary vein

cerebrovascular accident (CVA) blockage of blood flow to the brain; also called a stroke

circle of Willis (also, arterial circle) anastomosis located at the base of the brain that ensures continual blood supply; formed from branches of the internal carotid and vertebral arteries; supplies blood to the brain

circulatory shock also simply called shock; a life-threatening medical condition in which the circulatory system is unable to supply enough blood flow to provide adequate oxygen and other nutrients to the tissues to maintain cellular metabolism

common carotid artery right common carotid artery arises from the brachiocephalic artery, and the left common carotid arises from the aortic arch; gives rise to the external and internal carotid arteries; supplies the respective sides of the head and neck

common hepatic artery branch of the celiac trunk that forms the hepatic artery, the right gastric artery, and the cystic artery

common iliac artery branch of the aorta that leads to the internal and external iliac arteries

common iliac vein one of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior portion of the sacroiliac joint

compliance degree to which a blood vessel can stretch as opposed to being rigid

continuous capillary most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

cystic artery branch of the common hepatic artery; supplies blood to the gall bladder

deep femoral artery branch of the femoral artery; gives rise to the lateral circumflex arteries

deep femoral vein drains blood from the deeper portions of the thigh and leads to the femoral vein

descending aorta portion of the aorta that continues downward past the end of the aortic arch; subdivided into the thoracic aorta and the abdominal aorta

diastolic pressure lower number recorded when measuring arterial blood pressure; represents the minimal value corresponding to the pressure that remains during ventricular relaxation

digital arteries formed from the superficial and deep palmar arches; supply blood to the digits

blood within the body

hypovolemia abnormally low levels of fluid and blood within the body

hypovolemic shock type of circulatory shock caused by excessive loss of blood volume due to hemorrhage or possibly dehydration

hypoxia lack of oxygen supply to the tissues

inferior mesenteric artery branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum

inferior phrenic artery branch of the abdominal aorta; supplies blood to the inferior surface of the diaphragm

inferior vena cava large systemic vein that drains blood from areas largely inferior to the diaphragm; empties into the right atrium

intercostal artery branch of the thoracic aorta; supplies blood to the muscles of the thoracic cavity and vertebral column

intercostal vein drains the muscles of the thoracic wall and leads to the azygos vein

internal carotid artery arises from the common carotid artery and begins with the carotid sinus; goes through the carotid canal of the temporal bone to the base of the brain; combines with branches of the vertebral artery forming the arterial circle; supplies blood to the brain

internal elastic membrane membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

internal iliac artery branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provide blood to the uterus and vagina

internal iliac vein drains the pelvic organs and integument; formed from several smaller veins in the region; leads to the common iliac vein

internal jugular vein one of a pair of major veins located in the neck region that passes through the jugular foramen and canal, flows parallel to the common carotid artery that is more or less its counterpart; primarily drains blood from the brain, receives the superficial facial vein, and empties into the subclavian vein

internal thoracic artery (also, mammary artery) arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and the anterior chest wall

internal thoracic vein (also, internal mammary vein) drains the anterior surface of the chest wall and leads to the brachiocephalic vein

interstitial fluid colloidal osmotic pressure (IFCOP) pressure exerted by the colloids within the interstitial fluid

interstitial fluid hydrostatic pressure (IFHP) force exerted by the fluid in the tissue spaces

ischemia insufficient blood flow to the tissues

Korotkoff sounds noises created by turbulent blood flow through the vessels

lateral circumflex artery branch of the deep femoral artery; supplies blood to the deep muscles of the thigh and the ventral and lateral regions of the integument

lateral plantar artery arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot

left gastric artery branch of the celiac trunk; supplies blood to the stomach

lumbar arteries branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord

lumbar veins drain the lumbar portion of the abdominal wall and spinal cord; the superior lumbar veins drain into the azygos vein on the right or the hemiazygos vein on the left; blood from these vessels is returned to the superior vena cava rather than the inferior vena cava

lumen interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

maxillary vein drains blood from the maxillary region and leads to the external jugular vein

mean arterial pressure (MAP) average driving force of blood to the tissues; approximated by taking diastolic pressure and adding 1/3 of pulse pressure

medial plantar artery arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot

median antebrachial vein vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches

median cubital vein superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site for a blood draw

median sacral artery continuation of the aorta into the sacrum

mediastinal artery branch of the thoracic aorta; supplies blood to the mediastinum

metarteriole short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation blood flow through the capillaries

middle cerebral artery another branch of the internal carotid artery; supplies blood to the temporal and parietal lobes of the cerebrum

pulse pressure difference between the systolic and diastolic pressures

radial artery formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

radial vein parallels the radius and radial artery; arises from the palmar venous arches and leads to the brachial vein

reabsorption in the cardiovascular system, the movement of material from the interstitial fluid into the capillaries

renal artery branch of the abdominal aorta; supplies each kidney

renal vein largest vein entering the inferior vena cava; drains the kidneys and leads to the inferior vena cava

resistance any condition or parameter that slows or counteracts the flow of blood

respiratory pump increase in the volume of the thorax during inhalation that decreases air pressure, enabling venous blood to flow into the thoracic region, then exhalation increases pressure, moving blood into the atria

right gastric artery branch of the common hepatic artery; supplies blood to the stomach

sepsis (also, septicemia) organismal-level inflammatory response to a massive infection

septic shock (also, blood poisoning) type of shock that follows a massive infection resulting in organism-wide inflammation

sigmoid sinuses enlarged veins that receive blood from the transverse sinuses; flow through the jugular foramen and into the internal jugular vein

sinusoid capillary rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

skeletal muscle pump effect on increasing blood pressure within veins by compression of the vessel caused by the contraction of nearby skeletal muscle

small saphenous vein located on the lateral surface of the leg; drains blood from the superficial regions of the lower leg and foot, and leads to the popliteal vein

sphygmomanometer blood pressure cuff attached to a device that measures blood pressure

splenic artery branch of the celiac trunk; supplies blood to the spleen

straight sinus enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and flows into the left or right transverse sinus

subclavian artery right subclavian arises from the brachiocephalic artery, whereas the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system

subclavian vein located deep in the thoracic cavity; becomes the axillary vein as it enters the axillary region; drains the axillary and smaller local veins near the scapular region; leads to the brachiocephalic vein

subscapular vein drains blood from the subscapular region and leads to the axillary vein

superior mesenteric artery branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine

superior phrenic artery branch of the thoracic aorta; supplies blood to the superior surface of the diaphragm

superior sagittal sinus enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein

superior vena cava large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium

systolic pressure larger number recorded when measuring arterial blood pressure; represents the maximum value following ventricular contraction

temporal vein drains blood from the temporal region and leads to the external jugular vein

testicular artery branch of the abdominal aorta; will ultimately travel outside the body cavity to the testes and form one component of the spermatic cord

testicular vein drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein

thoracic aorta portion of the descending aorta superior to the aortic hiatus

thoroughfare channel continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

thyrocervical artery arises from the subclavian artery; supplies blood to the thyroid, the cervical

arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

20.2 Blood Flow, Blood Pressure, and Resistance

Blood flow is the movement of blood through a vessel, tissue, or organ. The slowing or blocking of blood flow is called resistance. Blood pressure is the force that blood exerts upon the walls of the blood vessels or chambers of the heart. The components of blood pressure include systolic pressure, which results from ventricular contraction, and diastolic pressure, which results from ventricular relaxation. Pulse pressure is the difference between systolic and diastolic measures, and mean arterial pressure is the "average" pressure of blood in the arterial system, driving blood into the tissues. Pulse, the expansion and recoiling of an artery, reflects the heartbeat. The variables affecting blood flow and blood pressure in the systemic circulation are cardiac output, compliance, blood volume, blood viscosity, and the length and diameter of the blood vessels. In the arterial system, vasodilation and vasoconstriction of the arterioles is a significant factor in systemic blood pressure: Slight vasodilation greatly decreases resistance and increases flow, whereas slight vasoconstriction greatly increases resistance and decreases flow. In the arterial system, as resistance increases, blood pressure increases and flow decreases. In the venous system, constriction increases blood pressure as it does in arteries; the increasing pressure helps to return blood to the heart. In addition, constriction causes the vessel lumen to become more rounded, decreasing resistance and increasing blood flow. Venoconstriction, while less important than arterial vasoconstriction, works with the skeletal muscle pump, the respiratory pump, and their valves to promote venous return to the heart.

20.3 Capillary Exchange

Small molecules can cross into and out of capillaries via simple or facilitated diffusion. Some large molecules can cross in vesicles or through clefts, fenestrations, or gaps between cells in capillary walls. However, the bulk flow of capillary and tissue fluid occurs via filtration and reabsorption. Filtration, the movement of fluid out of the capillaries, is driven by the CHP. Reabsorption, the influx of tissue fluid into the capillaries, is driven by the BCOP. Filtration predominates in the arterial end of the capillary; in the middle section, the opposing pressures are virtually identical so there is no net exchange, whereas reabsorption predominates at the venule end of the capillary. The hydrostatic and colloid osmotic pressures in the interstitial fluid are negligible in healthy circumstances.

20.4 Homeostatic Regulation of the Vascular System

Neural, endocrine, and autoregulatory mechanisms affect blood flow, blood pressure, and eventually perfusion of blood to body tissues. Neural mechanisms include the cardiovascular centers in the medulla oblongata, baroreceptors in the aorta and carotid arteries and right atrium, and associated chemoreceptors that monitor blood levels of oxygen, carbon dioxide, and hydrogen ions. Endocrine controls include epinephrine and norepinephrine, as well as ADH, the renin-angiotensin-aldosterone mechanism, ANH, and EPO. Autoregulation is the local control of vasodilation and constriction by chemical signals and the myogenic response. Exercise greatly improves cardiovascular function and reduces the risk of cardiovascular diseases, including hypertension, a leading cause of heart attacks and strokes. Significant hemorrhage can lead to a form of circulatory shock known as hypovolemic shock. Sepsis, obstruction, and widespread inflammation can also cause circulatory shock.

20.5 Circulatory Pathways

The right ventricle pumps oxygen-depleted blood into the pulmonary trunk and right and left pulmonary arteries, which carry it to the right and left lungs for gas exchange. Oxygen-rich blood is transported by pulmonary veins to the left atrium. The left ventricle pumps this blood into the aorta. The main regions of the aorta are the ascending aorta, aortic arch, and descending aorta, which is further divided into the thoracic and abdominal aorta. The coronary arteries branch from the ascending aorta. After oxygenating tissues in the capillaries, systemic blood is returned to the right atrium from the venous system via the superior vena cava, which drains most of the veins superior to the diaphragm, the inferior vena cava, which drains most of the veins inferior to the diaphragm, and the coronary veins via the coronary sinus. The hepatic portal system carries blood to the liver for processing before it enters circulation. Review the figures provided in this section for circulation of blood through the blood vessels.

13. Hydrostatic pressure is _____.
   a. greater than colloid osmotic pressure at the venous end of the capillary bed
   b. the pressure exerted by fluid in an enclosed space
   c. about zero at the midpoint of a capillary bed
   d. all of the above

14. Net filtration pressure is calculated by _____.
   a. adding the capillary hydrostatic pressure to the interstitial fluid hydrostatic pressure
   b. subtracting the fluid drained by the lymphatic vessels from the total fluid in the interstitial fluid
   c. adding the blood colloid osmotic pressure to the capillary hydrostatic pressure
   d. subtracting the blood colloid osmotic pressure from the capillary hydrostatic pressure

15. Which of the following statements is true?
   a. In one day, more fluid exits the capillary through filtration than enters through reabsorption.
   b. In one day, approximately 35 mm of blood are filtered and 7 mm are reabsorbed.
   c. In one day, the capillaries of the lymphatic system absorb about 20.4 liters of fluid.
   d. None of the above are true.

16. Clusters of neurons in the medulla oblongata that regulate blood pressure are known collectively as _____.
   a. baroreceptors
   b. angioreceptors
   c. the cardiomotor mechanism
   d. the cardiovascular center

17. In the renin-angiotensin-aldosterone mechanism, _____.
   a. decreased blood pressure prompts the release of renin from the liver
   b. aldosterone prompts increased urine output
   c. aldosterone prompts the kidneys to reabsorb sodium
   d. all of the above

18. In the myogenic response, _____.
   a. muscle contraction promotes venous return to the heart
   b. ventricular contraction strength is decreased
   c. vascular smooth muscle responds to stretch
   d. endothelins dilate muscular arteries

19. A form of circulatory shock common in young children with severe diarrhea or vomiting is _____.
   a. hypovolemic shock
   b. anaphylactic shock
   c. obstructive shock
   d. hemorrhagic shock

20. The coronary arteries branch off of the _____.
   a. aortic valve
   b. ascending aorta
   c. aortic arch
   d. thoracic aorta

21. Which of the following statements is true?
   a. The left and right common carotid arteries both branch off of the brachiocephalic trunk.
   b. The brachial artery is the distal branch of the axillary artery.
   c. The radial and ulnar arteries join to form the palmar arch.
   d. All of the above are true.

22. Arteries serving the stomach, pancreas, and liver all branch from the _____.
   a. superior mesenteric artery
   b. inferior mesenteric artery
   c. celiac trunk
   d. splenic artery

23. The right and left brachiocephalic veins _____.
   a. drain blood from the right and left internal jugular veins
   b. drain blood from the right and left subclavian veins
   c. drain into the superior vena cava
   d. all of the above are true

24. The hepatic portal system delivers blood from the digestive organs to the _____.
   a. liver
   b. hypothalamus
   c. spleen
   d. left atrium

25. Blood islands are _____.
   a. clusters of blood-filtering cells in the placenta
   b. masses of pluripotent stem cells scattered throughout the fetal bone marrow
   c. vascular tubes that give rise to the embryonic tubular heart
   d. masses of developing blood vessels and formed elements scattered throughout the embryonic disc

21.1 Anatomy of the Lymphatic and Immune Systems

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes “backs up” from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

INTERACTIVE LINK

Visit this website (http://openstax.org/l/lymphsystem) for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Structure of the Lymphatic System

The lymphatic vessels begin as a blind ending, or closed at one end, capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body (Figure 21.2).

FIGURE 21.2 Anatomy of the Lymphatic System Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body (Figure 21.3). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

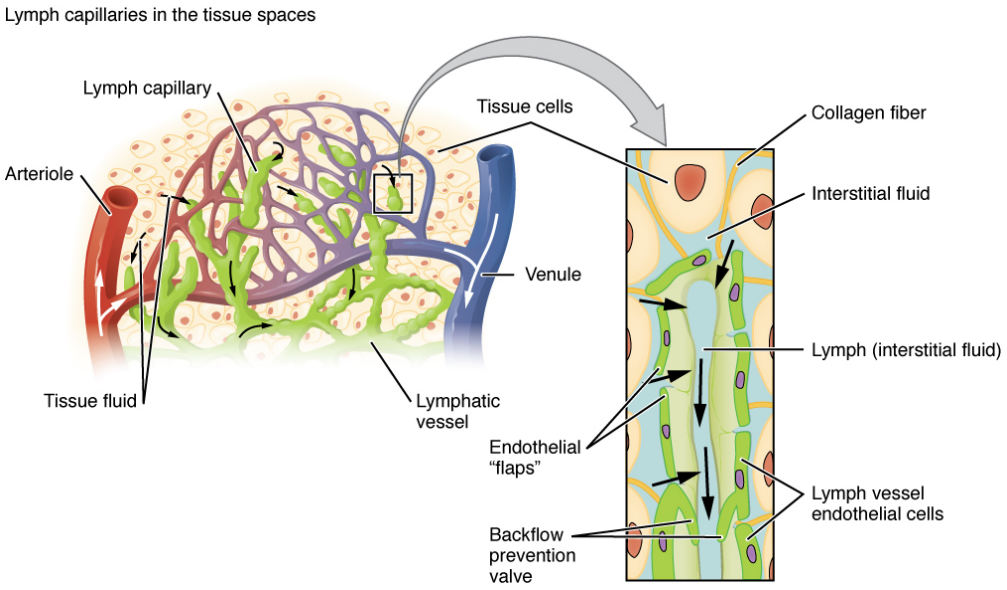


FIGURE 21.3 Lymphatic Capillaries Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see Figure 21.3). When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see Figure 21.3).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct (Figure 21.4). On the left side of the body, the remaining portions of the

intracellular pathogens such as viruses

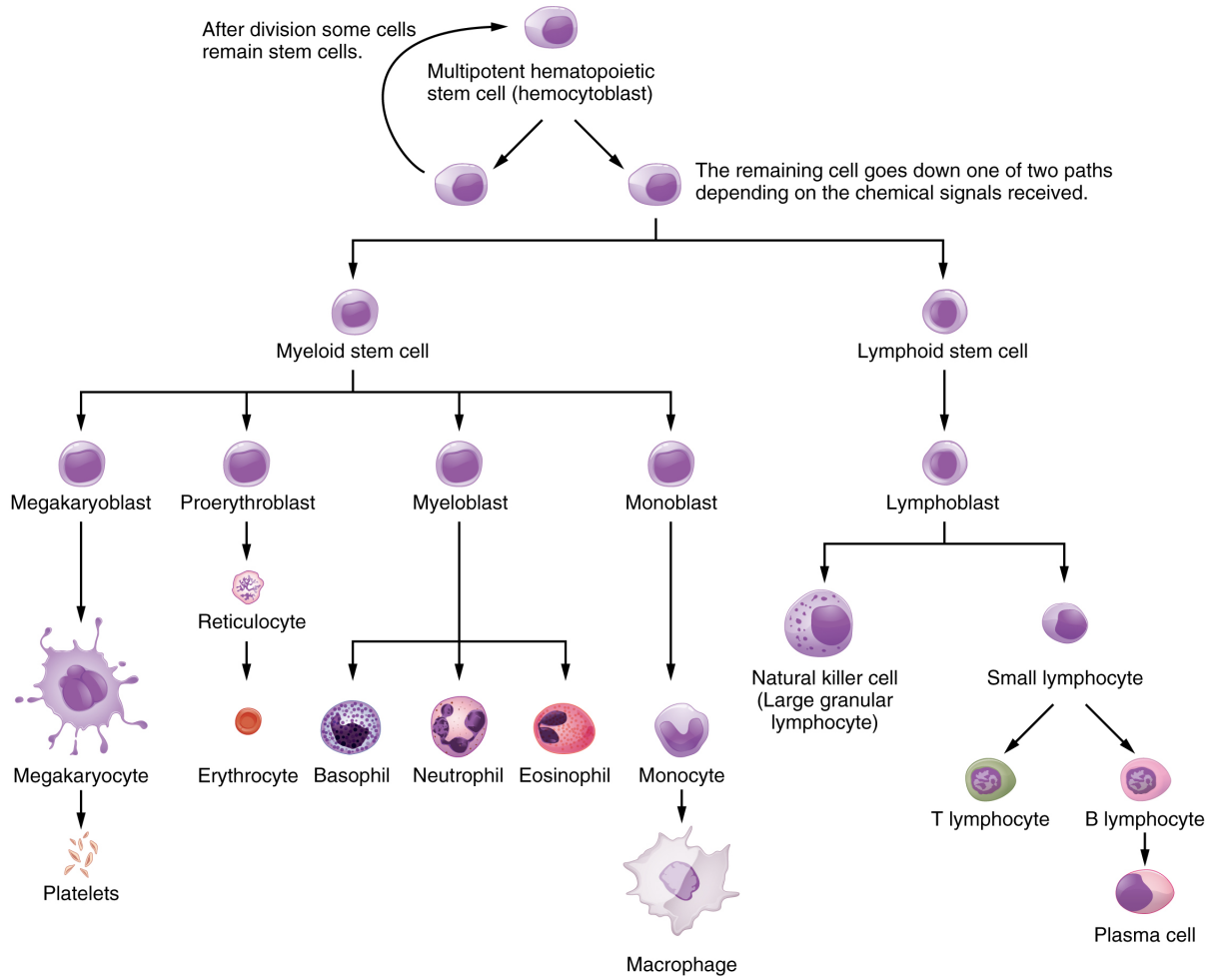


FIGURE 21.5 Hematopoietic System of the Bone Marrow All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses (Table 21.1). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B

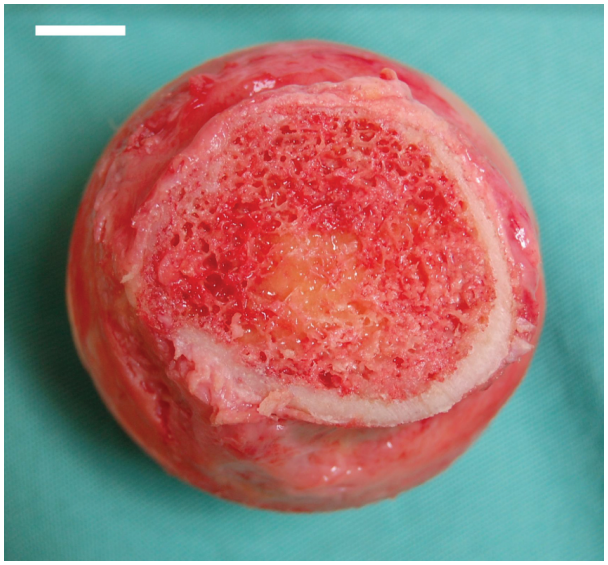


FIGURE 21.6 Bone Marrow Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart (Figure 21.7). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

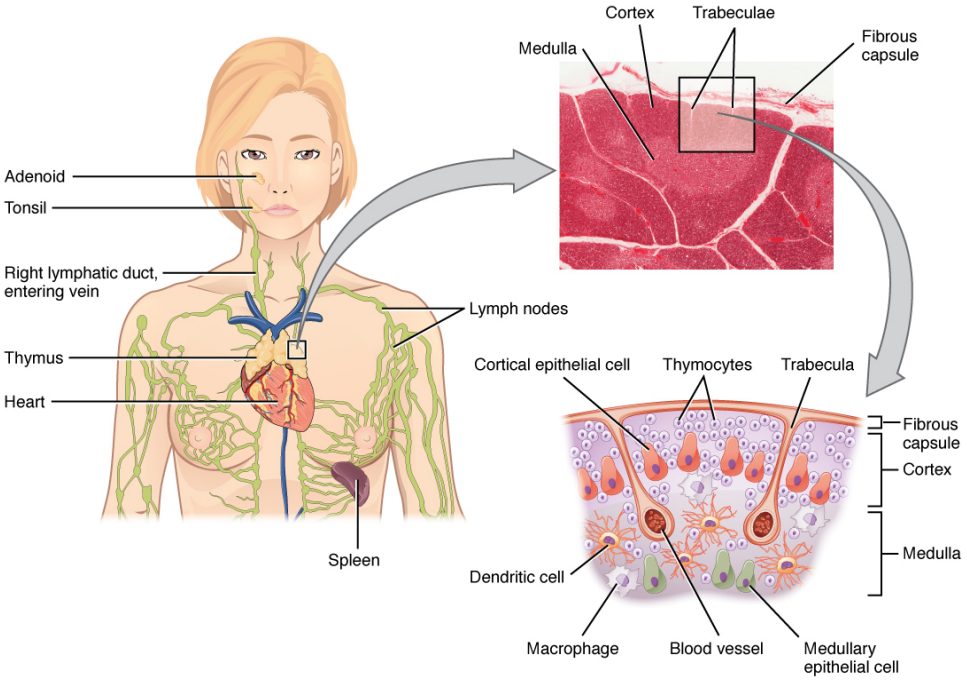


FIGURE 21.7 Location, Structure, and Histology of the Thymus The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/thymusMG) to explore the tissue sample in greater detail.

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is

site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

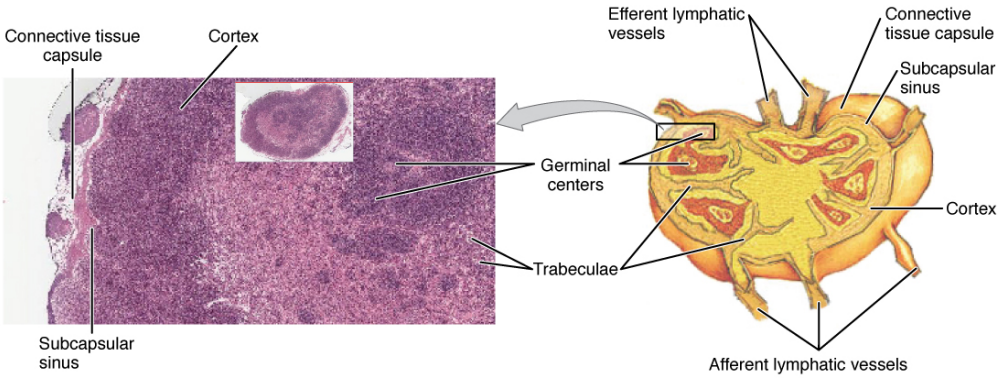


FIGURE 21.8 Structure and Histology of a Lymph Node Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/lymphnodeMG) to explore the tissue sample in greater detail.

The major routes into the lymph node are via **afferent lymphatic vessels** (see Figure 21.8). Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the **efferent lymphatic vessels**. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ (Figure 21.9). It is about 12 cm (5 in) long and is attached to the lateral border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the “filter of the blood” because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

tonsils—to help children's bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

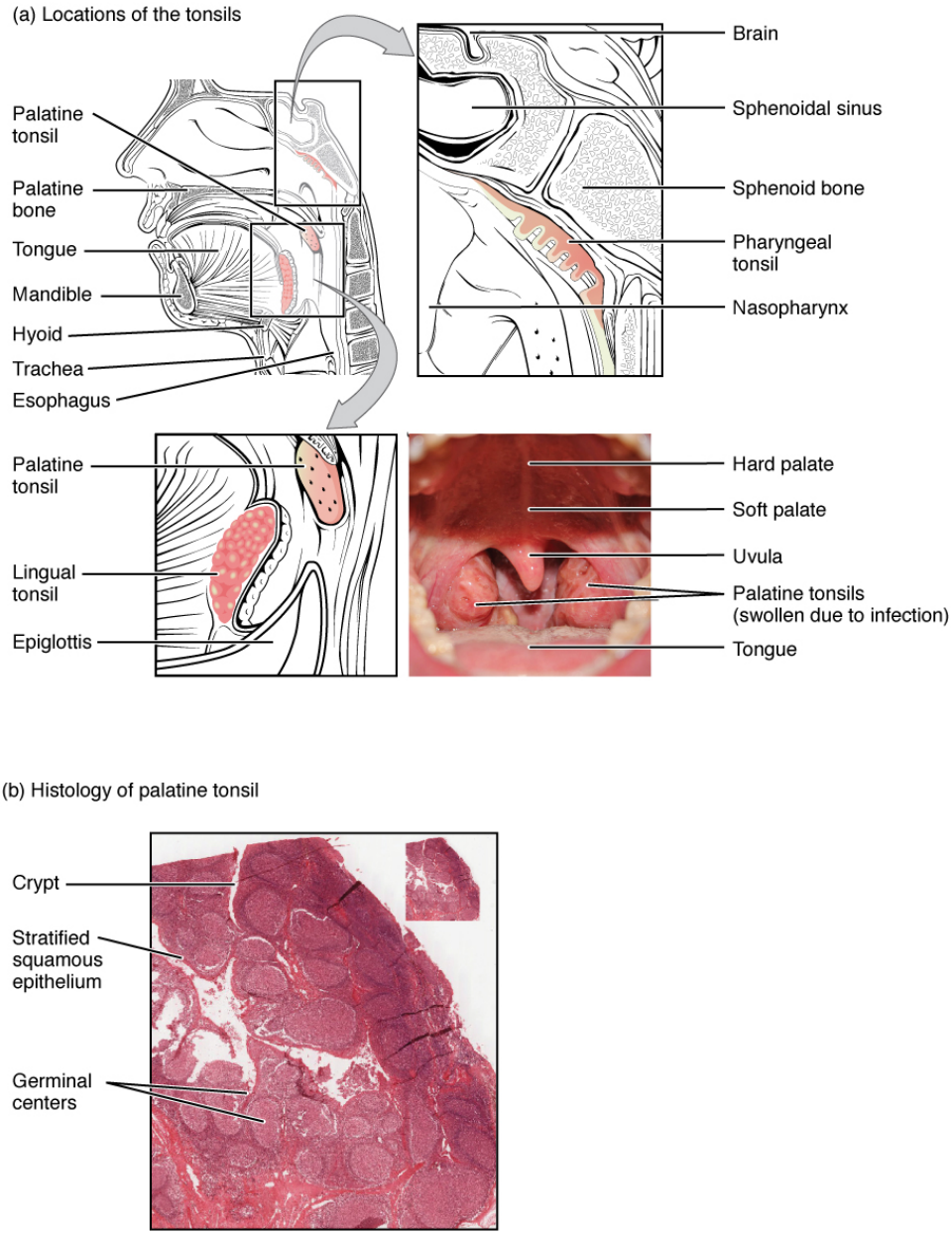


FIGURE 21.10 Locations and Histology of the Tonsils (a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

INTERACTIVE LINK

View the University of Michigan WebScope (http://openstax.org/l/tonsilMG) to explore the tissue sample in greater detail.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances (Figure 21.11). Peyer's patches contain

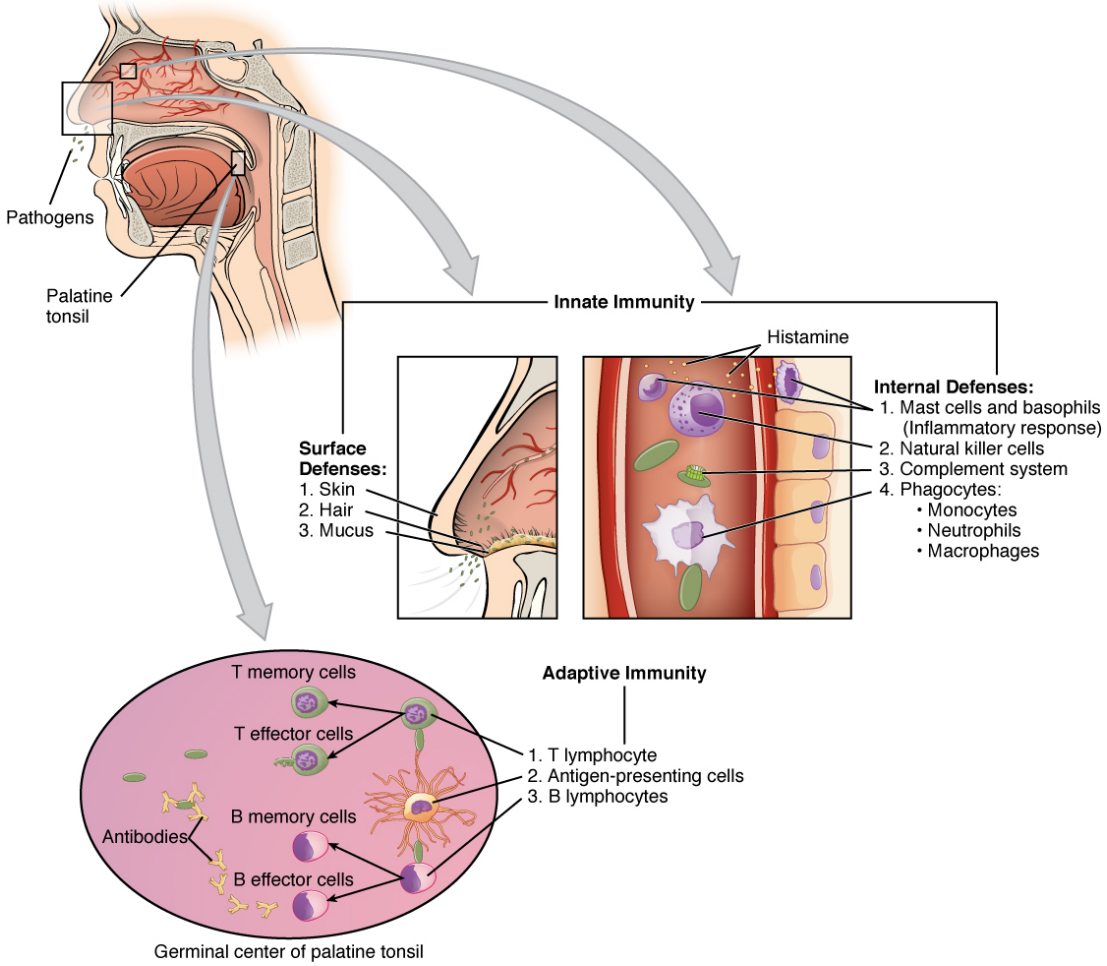


FIGURE 21.12 Cooperation between Innate and Adaptive Immune Responses The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter (Table 21.2). The primary barrier to the entrance of microorganisms into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

Barrier Defenses

Site	Specific defense	Protective aspect
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action

TABLE 21.2

rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System

Cell	Cell type	Primary location	Function in the innate immune response
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis
Neutrophil	Granulocyte	Blood	Phagocytosis
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell

TABLE 21.3

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or

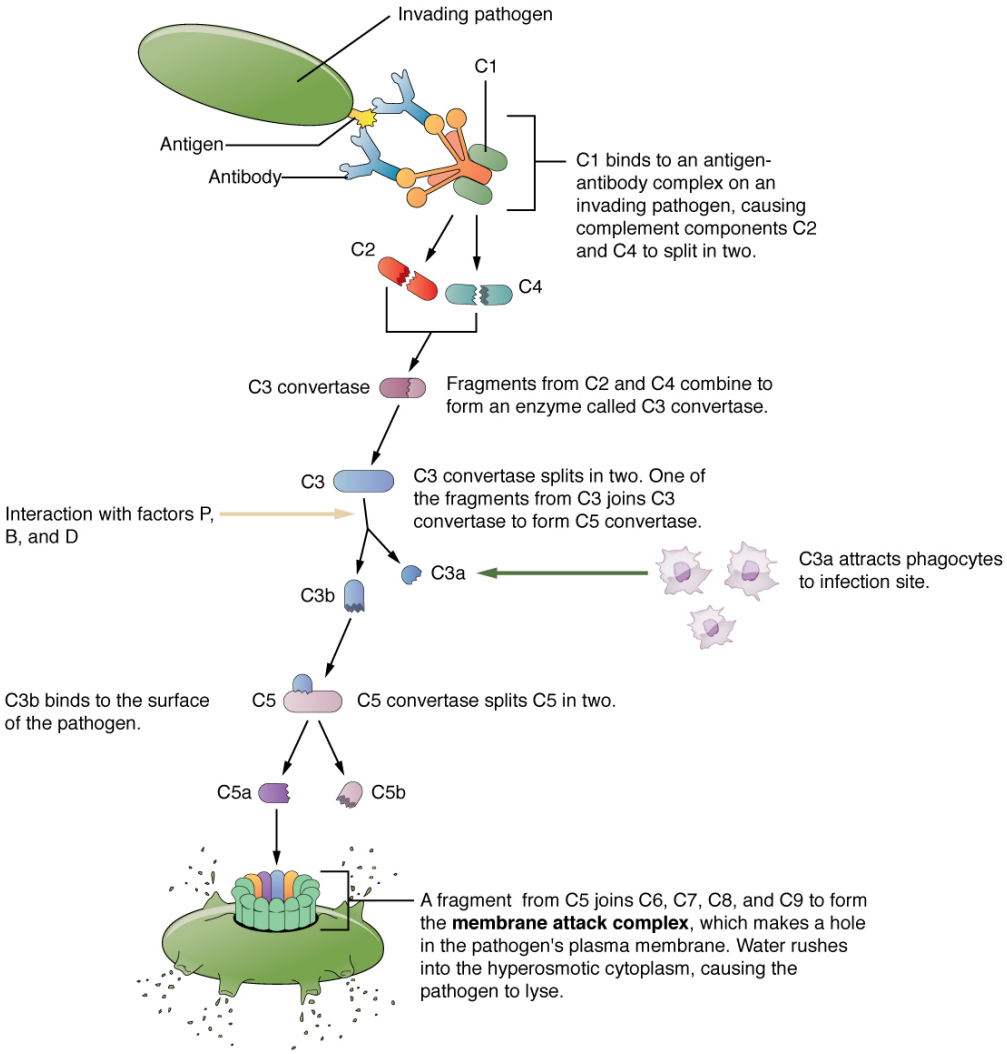


FIGURE 21.13 Complement Cascade and Function The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling (“loss of function” is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to

more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

21.3 The Adaptive Immune Response: T lymphocytes and Their Functional Types

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the advantages of the adaptive immune response over the innate immune response
- List the various characteristics of an antigen
- Describe the types of T cell antigen receptors
- Outline the steps of T cell development
- Describe the major T cell types and their functions

Innate immune responses (and early induced responses) are in many cases ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The specificity of the adaptive immune response—its ability to specifically recognize and make a response against a wide variety of pathogens—is its great strength. Antigens, the small chemical groups often associated with pathogens, are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as 10^{11}, or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? And what about the many specificities of T cells? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics.

Primary Disease and Immunological Memory

The immune system's first exposure to a pathogen is called a **primary adaptive response**. Symptoms of a first infection, called primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster than the primary response. The **secondary adaptive response** often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of **immunological memory**, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual's exposure to pathogens early in life spares the person from these diseases later in life.

Self Recognition

A third important feature of the adaptive immune response is its ability to distinguish between self-antigens, those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, there are mechanisms in place that prevent them from recognizing self-antigen, preventing a damaging immune response against the body. These mechanisms are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

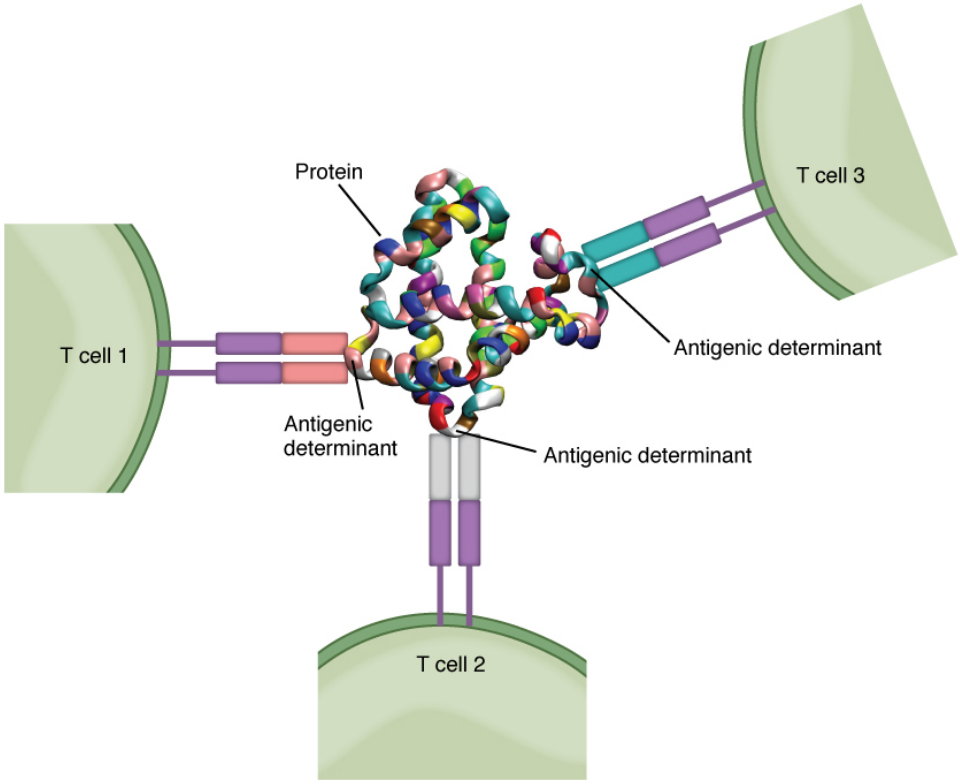


FIGURE 21.16 Antigenic Determinants A typical protein antigen has multiple antigenic determinants, shown by the ability of T cells with three different specificities to bind to different parts of the same antigen.

Antigen Processing and Presentation

Although Figure 21.16 shows T cell receptors interacting with antigenic determinants directly, the mechanism that T cells use to recognize antigens is, in reality, much more complex. T cells do not recognize free-floating or cell-bound antigens as they appear on the surface of the pathogen. They only recognize antigen on the surface of specialized cells called antigen-presenting cells. Antigens are internalized by these cells. **Antigen processing** is a mechanism that enzymatically cleaves the antigen into smaller pieces. The antigen fragments are then brought to the cell's surface and associated with a specialized type of antigen-presenting protein known as a **major histocompatibility complex (MHC)** molecule. The MHC is the cluster of genes that encode these antigen-presenting molecules. The association of the antigen fragments with an MHC molecule on the surface of a cell is known as **antigen presentation** and results in the recognition of antigen by a T cell. This association of antigen and MHC occurs inside the cell, and it is the complex of the two that is brought to the surface. The peptide-binding cleft is a small indentation at the end of the MHC molecule that is furthest away from the cell membrane; it is here that the processed fragment of antigen sits. MHC molecules are capable of presenting a variety of antigens, depending on the amino acid sequence, in their peptide-binding clefts. It is the combination of the MHC molecule and the fragment of the original peptide or carbohydrate that is actually physically recognized by the T cell receptor (Figure 21.17).

macrophages, dendritic cells, and B cells (Table 21.4).

Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis (see Figure 21.17), but their major function is to bring antigens to regional draining lymph nodes. The lymph nodes are the locations in which most T cell responses against pathogens of the interstitial tissues are mounted. Macrophages are found in the skin and in the lining of mucosal surfaces, such as the nasopharynx, stomach, lungs, and intestines. B cells may also present antigens to T cells, which are necessary for certain types of antibody responses, to be covered later in this chapter.

Classes of Antigen-presenting Cells

MHC	Cell type	Phagocytic?	Function
Class I	Many	No	Stimulates cytotoxic T cell immune response
Class II	Macrophage	Yes	Stimulates phagocytosis and presentation at primary infection site
Class II	Dendritic	Yes, in tissues	Brings antigens to regional lymph nodes
Class II	B cell	Yes, internalizes surface Ig and antigen	Stimulates antibody secretion by B cells

TABLE 21.4

T Cell Development and Differentiation

The process of eliminating T cells that might attack the cells of one's own body is referred to as **T cell tolerance**. While thymocytes are in the cortex of the thymus, they are referred to as "double negatives," meaning that they do not bear the CD4 or CD8 molecules that you can use to follow their pathways of differentiation (Figure 21.18). In the cortex of the thymus, they are exposed to cortical epithelial cells. In a process known as **positive selection**, double-negative thymocytes bind to the MHC molecules they observe on the thymic epithelia, and the MHC molecules of "self" are selected. This mechanism kills many thymocytes during T cell differentiation. In fact, only two percent of the thymocytes that enter the thymus leave it as mature, functional T cells.

Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing processed foreign antigen in association with a self-MHC molecule and begin dividing rapidly by mitosis. This proliferation of T cells is called **clonal expansion** and is necessary to make the immune response strong enough to effectively control a pathogen. How does the body select only those T cells that are needed against a specific pathogen? Again, the specificity of a T cell is based on the amino acid sequence and the three-dimensional shape of the antigen-binding site formed by the variable regions of the two chains of the T cell receptor (Figure 21.19). **Clonal selection** is the process of antigen binding only to those T cells that have receptors specific to that antigen. Each T cell that is activated has a specific receptor "hard-wired" into its DNA, and all of its progeny will have identical DNA and T cell receptors, forming clones of the original T cell.

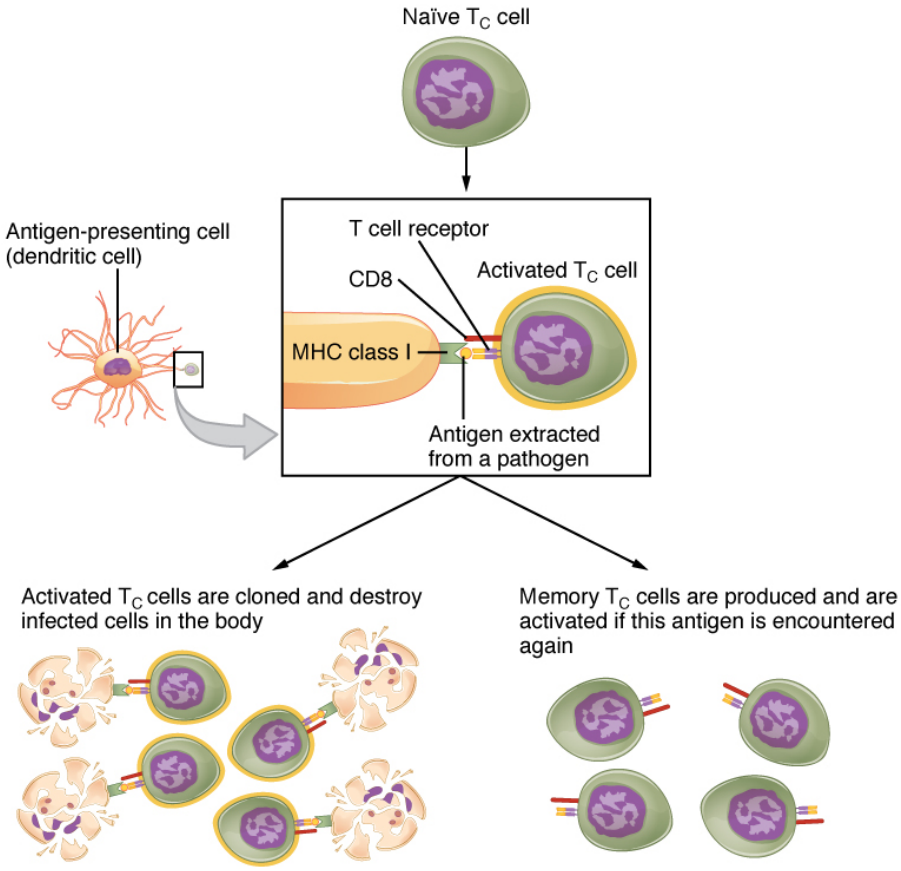


FIGURE 21.19 Clonal Selection and Expansion of T Lymphocytes Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

Clonal Selection and Expansion

The clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term clonal selection is not a complete description of the theory, as clonal expansion goes hand in glove with the selection process. The main tenet of the theory is that a typical individual has a multitude (10^{11}) of different types of T cell clones based on their receptors. In this use, a **clone** is a group of lymphocytes that share the same **antigen receptor**. Each clone is necessarily present in the body in low numbers. Otherwise, the body would not have room for lymphocytes with so many specificities.

Only those clones of lymphocytes whose receptors are activated by the antigen are stimulated to proliferate. Keep in mind that most antigens have multiple antigenic determinants, so a T cell response to a typical antigen involves a polyclonal response. A **polyclonal response** is the stimulation of multiple T cell clones. Once activated, the selected clones increase in number and make many copies of each cell type, each clone with its unique receptor. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection (see Figure 21.19).

Th1 cells are a type of helper T cell that secretes cytokines that regulate the immunological activity and development of a variety of cells, including macrophages and other types of T cells.

Th2 cells, on the other hand, are cytokine-secreting cells that act on B cells to drive their differentiation into plasma cells that make antibody. In fact, T cell help is required for antibody responses to most protein antigens, and these are called T cell-dependent antigens.

Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells by inducing apoptosis using the same mechanism as NK cells. They either express Fas ligand, which binds to the fas molecule on the target cell, or act by using perforins and granzymes contained in their cytoplasmic granules. As was discussed earlier with NK cells, killing a virally infected cell before the virus can complete its replication cycle results in the production of no infectious particles. As more Tc cells are developed during an immune response, they overwhelm the ability of the virus to cause disease. In addition, each Tc cell can kill more than one target cell, making them especially effective. Tc cells are so important in the antiviral immune response that some speculate that this was the main reason the adaptive immune response evolved in the first place.

Regulatory T Cells

Regulatory T cells (Treg), or suppressor T cells, are the most recently discovered of the types listed here, so less is understood about them. In addition to CD4, they bear the molecules CD25 and FOXP3. Exactly how they function is still under investigation, but it is known that they suppress other T cell immune responses. This is an important feature of the immune response, because if clonal expansion during immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on, and the types of pathogens they work against (see Table 21.5).

Functions of T Cell Types and Their Cytokines

T cell	Main target	Function	Pathogen	Surface marker	MHC	Cytokines or mediators
Tc	Infected cells	Cytotoxicity	Intracellular	CD8	Class I	Perforins, granzymes, and fas ligand
Th1	Macrophage	Helper inducer	Extracellular	CD4	Class II	Interferon-γ and TGF-β
Th2	B cell	Helper inducer	Extracellular	CD4	Class II	IL-4, IL-6, IL-10, and others
Treg	Th cell	Suppressor	None	CD4, CD25	?	TGF-β and IL-10

TABLE 21.5

21.4 The Adaptive Immune Response: B-lymphocytes and Antibodies

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain how B cells mature and how B cell tolerance develops
- Discuss how B cells are activated and differentiate into plasma cells
- Describe the structure of the antibody classes and their functions

Antibodies were the first component of the adaptive immune response to be characterized by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-

effector cells of the immune system have Fc receptors. Cells having these receptors can then bind to antibody-coated pathogens, greatly increasing the specificity of the effector cells. At the other end of the molecule are two identical antigen-binding sites.

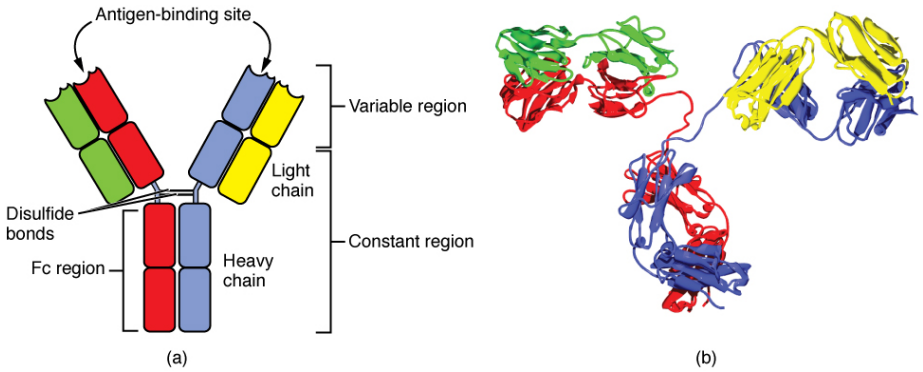


FIGURE 21.21 Antibody and IgG2 Structures The typical four chain structure of a generic antibody (a) and the corresponding three-dimensional structure of the antibody IgG2 (b). (credit b: modification of work by Tim Vickers)

Five Classes of Antibodies and their Functions

In general, antibodies have two basic functions. They can act as the B cell antigen receptor or they can be secreted, circulate, and bind to a pathogen, often labeling it for identification by other forms of the immune response. Of the five antibody classes, notice that only two can function as the antigen receptor for naïve B cells: IgM and **IgD** (Figure 21.22). Mature B cells that leave the bone marrow express both IgM and IgD, but both antibodies have the same antigen specificity. Only IgM is secreted, however, and no other nonreceptor function for IgD has been discovered.

The Five Immunoglobulin (Ig) Classes

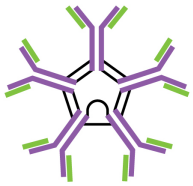
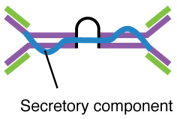
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

FIGURE 21.22 Five Classes of Antibodies

IgM consists of five four-chain structures (20 total chains with 10 identical antigen-binding sites) and is thus the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its 10 antigen-

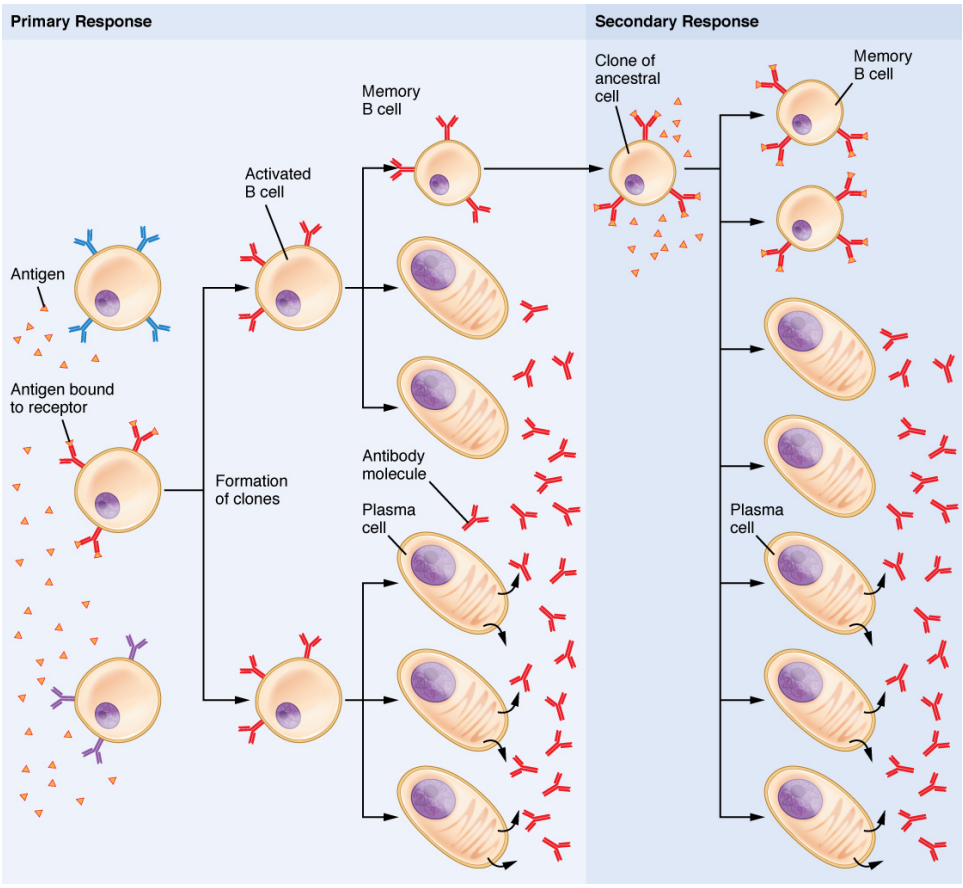


FIGURE 21.23 Clonal Selection of B Cells During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses.

Primary versus Secondary B Cell Responses

Primary and secondary responses as they relate to T cells were discussed earlier. This section will look at these responses with B cells and antibody production. Because antibodies are easily obtained from blood samples, they are easy to follow and graph (Figure 21.24). As you will see from the figure, the primary response to an antigen (representing a pathogen) is delayed by several days. This is the time it takes for the B cell clones to expand and differentiate into plasma cells. The level of antibody produced is low, but it is sufficient for immune protection. The second time a person encounters the same antigen, there is no time delay, and the amount of antibody made is much higher. Thus, the secondary antibody response overwhelms the pathogens quickly and, in most situations, no symptoms are felt. When a different antigen is used, another primary response is made with its low antibody levels and time delay.

INTERACTIVE LINK

Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video (http://openstax.org/l/immunity) to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

T cell-dependent versus T cell-independent Antigens

As discussed previously, Th2 cells secrete cytokines that drive the production of antibodies in a B cell, responding to complex antigens such as those made by proteins. On the other hand, some antigens are T cell independent. A **T cell-independent antigen** usually is in the form of repeated carbohydrate moieties found on the cell walls of bacteria. Each antibody on the B cell surface has two binding sites, and the repeated nature of T cell-independent antigen leads to crosslinking of the surface antibodies on the B cell. The crosslinking is enough to activate it in the absence of T cell cytokines.

A **T cell-dependent antigen**, on the other hand, usually is not repeated to the same degree on the pathogen and thus does not crosslink surface antibody with the same efficiency. To elicit a response to such antigens, the B and T cells must come close together (Figure 21.25). The B cell must receive two signals to become activated. Its surface immunoglobulin must recognize native antigen. Some of this antigen is internalized, processed, and presented to the Th2 cells on a class II MHC molecule. The T cell then binds using its antigen receptor and is activated to secrete cytokines that diffuse to the B cell, finally activating it completely. Thus, the B cell receives signals from both its surface antibody and the T cell via its cytokines, and acts as a professional antigen-presenting cell in the process.

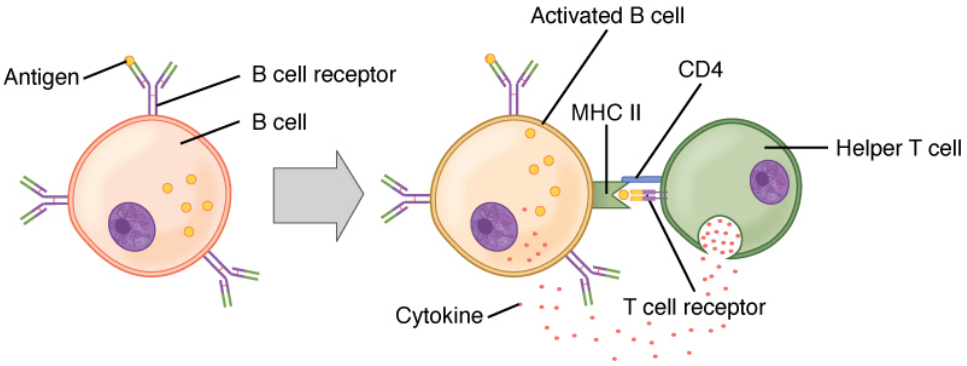


FIGURE 21.25 T and B Cell Binding To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell's cytokines.

21.5 The Immune Response against Pathogens

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain the development of immunological competence
- Describe the mucosal immune response
- Discuss immune responses against bacterial, viral, fungal, and animal pathogens
- Describe different ways pathogens evade immune responses

Now that you understand the development of mature, naïve B cells and T cells, and some of their major functions, how do all of these various cells, proteins, and cytokines come together to actually resolve an infection? Ideally, the immune response will rid the body of a pathogen entirely. The adaptive immune response, with its rapid clonal expansion, is well suited to this purpose. Think of a primary infection as a race between the pathogen and the immune system. The pathogen bypasses barrier defenses and starts multiplying in the host's body. During the first 4 to 5 days, the innate immune response will partially control, but not stop, pathogen growth. As the adaptive immune response gears up, however, it will begin to clear the pathogen from the body, while at the same time becoming stronger and stronger. When following antibody responses in patients with a particular disease such as a virus, this clearance is referred to as seroconversion (sero- = "serum"). **Seroconversion** is the reciprocal relationship between virus levels in the blood and antibody levels. As the antibody levels rise, the virus levels decline, and this is a sign that the immune response is being at least partially effective (partially, because in many diseases, seroconversion

pathogen to bind to receptors. Neutralization, which occurs in the blood, lymph, and other body fluids and secretions, protects the body constantly. Neutralizing antibodies are the basis for the disease protection offered by vaccines. Vaccinations for diseases that commonly enter the body via mucous membranes, such as influenza, are usually formulated to enhance IgA production.

Immune responses in some mucosal tissues such as the Peyer's patches (see Figure 21.11) in the small intestine take up particulate antigens by specialized cells known as microfold or M cells (Figure 21.27). These cells allow the body to sample potential pathogens from the intestinal lumen. Dendritic cells then take the antigen to the regional lymph nodes, where an immune response is mounted.

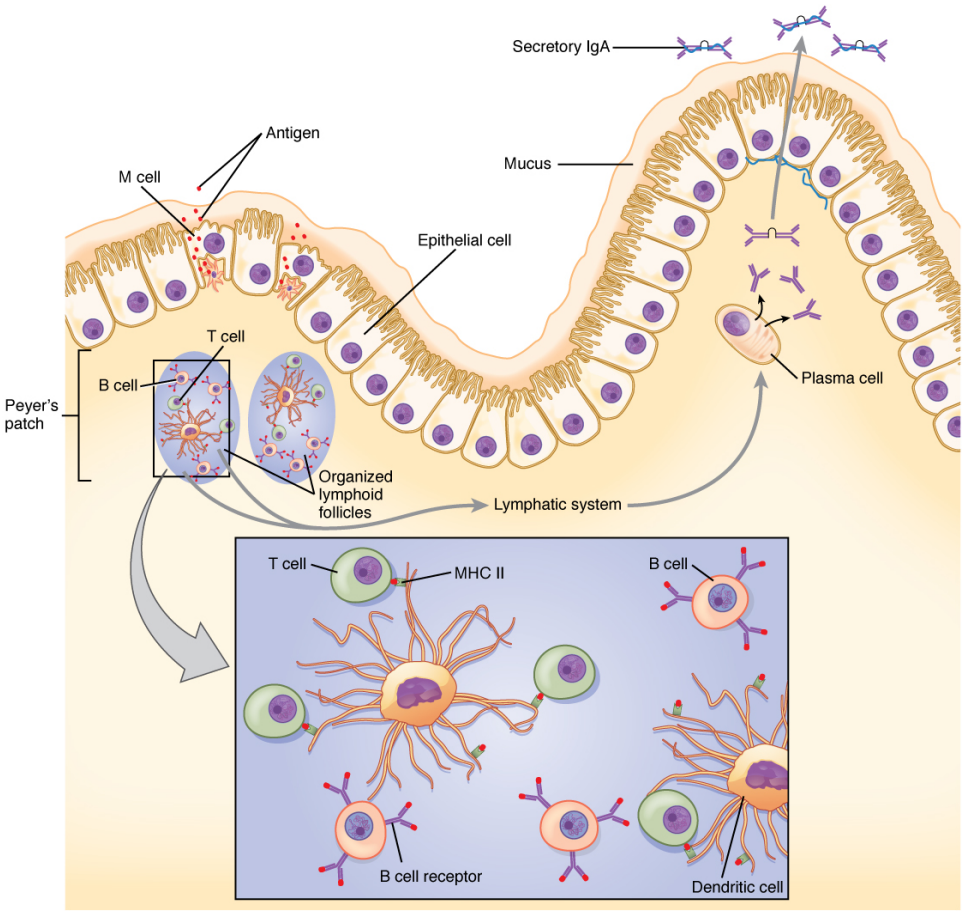


FIGURE 21.27 IgA Immunity The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that immune responses can be mounted.

Defenses against Bacteria and Fungi

The body fights bacterial pathogens with a wide variety of immunological mechanisms, essentially trying to find one that is effective. Bacteria such as *Mycobacterium leprae*, the cause of leprosy, are resistant to lysosomal enzymes and can persist in macrophage organelles or escape into the cytosol. In such situations, infected macrophages receiving cytokine signals from Th1 cells turn on special metabolic pathways. **Macrophage oxidative metabolism** is hostile to intracellular bacteria, often relying on the production of nitric oxide to kill the bacteria inside the macrophage.

Fungal infections, such as those from *Aspergillus*, *Candida*, and *Pneumocystis*, are largely opportunistic infections that take advantage of suppressed immune responses. Most of the same immune mechanisms effective against bacteria have similar effects on fungi, both of which have characteristic cell wall structures that protect their cells.

Defenses against Parasites

Worm parasites such as helminths are seen as the primary reason why the mucosal immune response, IgE-mediated allergy and asthma, and eosinophils evolved. These parasites were at one time very common in human

21.6 Diseases Associated with Depressed or Overactive Immune Responses

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss inherited and acquired immunodeficiencies
- Explain the four types of hypersensitivity and how they differ
- Give an example of how autoimmune disease breaks tolerance

This section is about how the immune system goes wrong. When it goes haywire, and becomes too weak or too strong, it leads to a state of disease. The factors that maintain immunological homeostasis are complex and incompletely understood.

Immunodeficiencies

As you have seen, the immune system is quite complex. It has many pathways using many cell types and signals. Because it is so complex, there are many ways for it to go wrong. Inherited immunodeficiencies arise from gene mutations that affect specific components of the immune response. There are also acquired immunodeficiencies with potentially devastating effects on the immune system, such as HIV.

Inherited Immunodeficiencies

A list of all inherited immunodeficiencies is well beyond the scope of this book. The list is almost as long as the list of cells, proteins, and signaling molecules of the immune system itself. Some deficiencies, such as those for complement, cause only a higher susceptibility to some Gram-negative bacteria. Others are more severe in their consequences. Certainly, the most serious of the inherited immunodeficiencies is **severe combined immunodeficiency disease (SCID)**. This disease is complex because it is caused by many different genetic defects. What groups them together is the fact that both the B cell and T cell arms of the adaptive immune response are affected.

Children with this disease usually die of opportunistic infections within their first year of life unless they receive a bone marrow transplant. Such a procedure had not yet been perfected for David Vetter, the “boy in the bubble,” who was treated for SCID by having to live almost his entire life in a sterile plastic cocoon for the 12 years before his death from infection in 1984. One of the features that make bone marrow transplants work as well as they do is the proliferative capability of hematopoietic stem cells of the bone marrow. Only a small amount of bone marrow from a healthy donor is given intravenously to the recipient. It finds its own way to the bone where it populates it, eventually reconstituting the patient’s immune system, which is usually destroyed beforehand by treatment with radiation or chemotherapeutic drugs.

New treatments for SCID using gene therapy, inserting nondefective genes into cells taken from the patient and giving them back, have the advantage of not needing the tissue match required for standard transplants. Although not a standard treatment, this approach holds promise, especially for those in whom standard bone marrow transplantation has failed.

Human Immunodeficiency Virus/AIDS

Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of $CD4^+$ cells, especially helper T cells, decline steadily, until at some point, the immune response is so weak that opportunistic disease and eventually death result. HIV uses CD4 as the receptor to get inside cells, but it also needs a co-receptor, such as CCR5 or CXCR4. These co-receptors, which usually bind to chemokines, present another target for anti-HIV drug development. Although other antigen-presenting cells are

Most allergens are in themselves nonpathogenic and therefore innocuous. Some individuals develop mild allergies, which are usually treated with antihistamines. Others develop severe allergies that may cause anaphylactic shock, which can potentially be fatal within 20 to 30 minutes if untreated. This drop in blood pressure (shock) with accompanying contractions of bronchial smooth muscle is caused by systemic mast cell degranulation when an allergen is eaten (for example, shellfish and peanuts), injected (by a bee sting or being administered penicillin), or inhaled (asthma). Because epinephrine raises blood pressure and relaxes bronchial smooth muscle, it is routinely used to counteract the effects of anaphylaxis and can be lifesaving. Patients with known severe allergies are encouraged to keep automatic epinephrine injectors with them at all times, especially when away from easy access to hospitals.

Allergists use skin testing to identify allergens in type I hypersensitivity. In skin testing, allergen extracts are injected into the epidermis, and a positive result of a soft, pale swelling at the site surrounded by a red zone (called the wheal and flare response), caused by the release of histamine and the granule mediators, usually occurs within 30 minutes. The soft center is due to fluid leaking from the blood vessels and the redness is caused by the increased blood flow to the area that results from the dilation of local blood vessels at the site.

Type II and Type III Hypersensitivities

Type II hypersensitivity, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis (see section on transplantation). **Type III hypersensitivity** occurs with diseases such as systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings. These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.

Delayed (Type IV) Hypersensitivity

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called **sensitization**, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages. A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal. A much more severe case of contact sensitivity is poison ivy, but many of the harshest symptoms of the reaction are associated with the toxicity of its oils and are not T cell mediated.

Autoimmune Responses

The worst cases of the immune system over-reacting are autoimmune diseases. Somehow, tolerance breaks down and the immune systems in individuals with these diseases begin to attack their own bodies, causing significant damage. The trigger for these diseases is, more often than not, unknown, and the treatments are usually based on resolving the symptoms using immunosuppressive and anti-inflammatory drugs such as steroids. These diseases can be localized and crippling, as in rheumatoid arthritis, or diffuse in the body with multiple symptoms that differ in different individuals, as is the case with systemic lupus erythematosus (Figure 21.29).

Disease	Autoantigen	Symptoms
Myasthenia gravis	Acetylcholine receptor in neuromuscular junctions	Debilitating muscle weakness
Rheumatoid arthritis	Joint capsule antigens	Chronic inflammation of joints

TABLE 21.7

21.7 Transplantation and Cancer Immunology

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. **Tissue typing** is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.

The Rh Factor

Red blood cells can be typed based on their surface antigens. ABO blood type, in which individuals are type A, B, AB, or O according to their genetics, is one example. A separate antigen system seen on red blood cells is the Rh antigen. When someone is “A positive” for example, the positive refers to the presence of the Rh antigen, whereas someone who is “A negative” would lack this molecule.

An interesting consequence of Rh factor expression is seen in **erythroblastosis fetalis**, a hemolytic disease of the newborn (Figure 21.30). This disease occurs when people negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the birth parent makes a primary anti-Rh antibody response to the fetal blood cells that enter the pregnant person's bloodstream. If the same parent has a second Rh-positive child, IgG antibodies against Rh-positive blood mounted during this secondary response cross the placenta and attack the fetal blood, causing anemia. This is a consequence of the fact that the fetus is not genetically identical to the birth parent, and thus the parent is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the pregnant person during the first and subsequent births, destroying any fetal blood that might enter their system and preventing the immune response.

Partial Table of Alleles of the Human MHC (Class I)

Gene	# of alleles	# of possible MHC I protein components
A	2132	1527
B	2798	2110
C	1672	1200
E	11	3
F	22	4
G	50	16

TABLE 21.8

Partial Table of Alleles of the Human MHC (Class II)

Gene	# of alleles	# of possible MHC II protein components
DRA	7	2
DRB	1297	958
DQA1	49	31
DQB1	179	128
DPA1	36	18
DPB1	158	136
DMA	7	4
DMB	13	7
DOA	12	3
DOB	13	5

TABLE 21.9

Immunosuppressive drugs such as cyclosporine A have made transplants more successful, but matching the MHC molecules is still key. In humans, there are six MHC molecules that show the most polymorphisms, three class I molecules (A, B, and C) and three class II molecules called DP, DQ, and DR. A successful transplant usually requires a match between at least 3–4 of these molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to share MHC molecules than unrelated individuals do. In fact, due to the extensive polymorphisms in these MHC molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

Everyday Connection

How Stress Affects the Immune Response: The Connections between the Immune, Nervous, and Endocrine Systems of the Body

The immune system cannot exist in isolation. After all, it has to protect the entire body from infection. Therefore, the immune system is required to interact with other organ systems, sometimes in complex ways. Thirty years of research focusing on the connections between the immune system, the central nervous system, and the endocrine system have led to a new science with the unwieldy name of called **psychoneuroimmunology**. The physical connections between these systems have been known for centuries: All primary and secondary organs are connected to sympathetic nerves. What is more complex, though, is the interaction of neurotransmitters, hormones, cytokines, and other soluble signaling molecules, and the mechanism of "crosstalk" between the systems. For example, white blood cells, including lymphocytes and phagocytes, have receptors for various neurotransmitters released by associated neurons. Additionally, hormones such as cortisol (naturally produced by the adrenal cortex) and prednisone (synthetic) are well known for their abilities to suppress T cell immune mechanisms, hence, their prominent use in medicine as long-term, anti-inflammatory drugs.

One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception (Table 21.10).

Effects of Stress on Body Systems

System	Stress-related illness
Integumentary system	Acne, rashes, irritation
Nervous system	Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance
Muscular and skeletal systems	Muscle and joint pain, neck and shoulder pain
Circulatory system	Increased heart rate, hypertension, increased probability of heart attacks
Digestive system	Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss
Immune system	Depressed ability to fight infections
Male reproductive system	Lowered sperm production, impotence, reduced sexual desire
Female reproductive system	Irregular menstrual cycle, reduced sexual desire

TABLE 21.10

Key Terms

active immunity immunity developed from an individual's own immune system
acute inflammation inflammation occurring for a limited time period; rapidly developing
adaptive immune response relatively slow but very specific and effective immune response controlled by lymphocytes
afferent lymphatic vessels lead into a lymph node
antibody antigen-specific protein secreted by plasma cells; immunoglobulin
antigen molecule recognized by the receptors of B and T lymphocytes
antigen presentation binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule
antigen processing internalization and digestion of antigen in an antigen-presenting cell
antigen receptor two-chain receptor by which lymphocytes recognize antigen
antigenic determinant (also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor
B cells lymphocytes that act by differentiating into an antibody-secreting plasma cell
barrier defenses antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection
bone marrow tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes
bronchus-associated lymphoid tissue (BALT) lymphoid nodule associated with the respiratory tract
central tolerance B cell tolerance induced in immature B cells of the bone marrow
chemokine soluble, long-range, cell-to-cell communication molecule
chronic inflammation inflammation occurring for long periods of time
chyle lipid-rich lymph inside the lymphatic capillaries of the small intestine
cisterna chyli bag-like vessel that forms the beginning of the thoracic duct
class switching ability of B cells to change the class of antibody they produce without altering the specificity for antigen
clonal anergy process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional
clonal deletion removal of self-reactive B cells by inducing apoptosis
clonal expansion growth of a clone of selected lymphocytes
clonal selection stimulating growth of lymphocytes that have specific receptors
clone group of lymphocytes sharing the same antigen receptor
complement enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria
constant region domain part of a lymphocyte antigen receptor that does not vary much between different receptor types
cytokine soluble, short-range, cell-to-cell communication molecule
cytotoxic T cells (Tc) T lymphocytes with the ability to induce apoptosis in target cells
delayed hypersensitivity (type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate
early induced immune response includes antimicrobial proteins stimulated during the first several days of an infection
effector T cells immune cells with a direct, adverse effect on a pathogen
efferent lymphatic vessels lead out of a lymph node
erythroblastosis fetalis disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood
fas ligand molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis
Fc region in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules
germinal centers clusters of rapidly proliferating B cells found in secondary lymphoid tissues
graft-versus-host disease in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient
granzyme apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells
heavy chain larger protein chain of an antibody
helper T cells (Th) T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes
high endothelial venules vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node
histamine vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

thymus that interact with self, but not non-self, MHC molecules

primary adaptive response immune system's response to the first exposure to a pathogen

primary lymphoid organ site where lymphocytes mature and proliferate; red bone marrow and thymus gland

psychoneuroimmunology study of the connections between the immune, nervous, and endocrine systems

regulatory T cells (Treg) (also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

right lymphatic duct drains lymph fluid from the upper right side of body into the right subclavian vein

secondary adaptive response immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

secondary lymphoid organs sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

sensitization first exposure to an antigen

seroconversion clearance of pathogen in the serum and the simultaneous rise of serum antibody

severe combined immunodeficiency disease (SCID) genetic mutation that affects both T cell and B cell arms of the immune response

spleen secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

T cell tolerance process during T cell differentiation where most T cells that recognize antigens from one's own body are destroyed

T cell-dependent antigen antigen that binds to B cells, which requires signals from T cells to make antibody

T cell-independent antigen binds to B cells, which do not require signals from T cells to make antibody

Th1 cells cells that secrete cytokines that enhance the activity of macrophages and other cells

Th2 cells cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

thoracic duct large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte immature T cell found in the thymus

thymus primary lymphoid organ; where T lymphocytes proliferate and mature

tissue typing typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure

tonsils lymphoid nodules associated with the nasopharynx

type I hypersensitivity immediate response mediated by mast cell degranulation caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface

type II hypersensitivity cell damage caused by the binding of antibody and the activation of complement, usually against red blood cells

type III hypersensitivity damage to tissues caused by the deposition of antibody-antigen (immune) complexes followed by the activation of complement

variable region domain part of a lymphocyte antigen receptor that varies considerably between different receptor types

Chapter Review

21.1 Anatomy of the Lymphatic and Immune Systems

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are site in which mature lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

21.2 Barrier Defenses and the Innate Immune Response

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities

3. Visit this website (http://openstax.org/l/chemotaxis) to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

4. Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video (http://openstax.org/l/immunity) to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

Review Questions

5. Which of the following cells is phagocytic?
   a. plasma cell
   b. macrophage
   c. B cell
   d. NK cell

6. Which structure allows lymph from the lower right limb to enter the bloodstream?
   a. thoracic duct
   b. right lymphatic duct
   c. right lymphatic trunk
   d. left lymphatic trunk

7. Which of the following cells is important in the innate immune response?
   a. B cells
   b. T cells
   c. macrophages
   d. plasma cells

8. Which of the following cells would be most active in early, antiviral immune responses the first time one is exposed to pathogen?
   a. macrophage
   b. T cell
   c. neutrophil
   d. natural killer cell

9. Which of the lymphoid nodules is most likely to see food antigens first?
   a. tonsils
   b. Peyer's patches
   c. bronchus-associated lymphoid tissue
   d. mucosa-associated lymphoid tissue

10. Which of the following signs is *not* characteristic of inflammation?
    a. redness
    b. pain
    c. cold
    d. swelling

11. Which of the following is *not* important in the antiviral innate immune response?
    a. interferons
    b. natural killer cells
    c. complement
    d. microphages

12. Enhanced phagocytosis of a cell by the binding of a specific protein is called _____.
    a. endocytosis
    b. opsonization
    c. anaphylaxis
    d. complement activation

13. Which of the following leads to the redness of inflammation?
    a. increased vascular permeability
    b. anaphylactic shock
    c. increased blood flow
    d. complement activation

14. T cells that secrete cytokines that help antibody responses are called _____.
    a. Th1
    b. Th2
    c. regulatory T cells
    d. thymocytes

15. The taking in of antigen and digesting it for later presentation is called _____.
    a. antigen presentation
    b. antigen processing
    c. endocytosis
    d. exocytosis

16. Why is clonal expansion so important?
    a. to select for specific cells
    b. to secrete cytokines
    c. to kill target cells
    d. to increase the numbers of specific cells

17. The elimination of self-reactive thymocytes is called _____.
    a. positive selection.
    b. negative selection.
    c. tolerance.
    d. clonal selection.

34. Which of the following terms means “many genes”?
   a. polymorphism
   b. polygeny
   c. polypeptide
   d. multiple alleles

35. Why do we have natural antibodies?
   a. We don’t know why.
   b. immunity to environmental bacteria
   c. immunity to transplants
   d. from clonal selection

36. Which type of cancer is associated with HIV disease?
   a. Kaposi’s sarcoma
   b. melanoma
   c. lymphoma
   d. renal cell carcinoma

37. How does cyclosporine A work?
   a. suppresses antibodies
   b. suppresses T cells
   c. suppresses macrophages
   d. suppresses neutrophils

38. What disease is associated with bone marrow transplants?
   a. diabetes mellitus type I
   b. melanoma
   c. headache
   d. graft-versus-host disease

Critical Thinking Questions

39. Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.

40. Describe the process of inflammation in an area that has been traumatized, but not infected.

41. Describe two early induced responses and what pathogens they affect.

42. Describe the processing and presentation of an intracellular antigen.

43. Describe clonal selection and expansion.

44. Describe how secondary B cell responses are developed.

45. Describe the role of IgM in immunity.

46. Describe how seroconversion works in HIV disease.

47. Describe tuberculosis and the innocent bystander effect.

48. Describe anaphylactic shock in someone sensitive to peanuts?

49. Describe rheumatic fever and how tolerance is broken.

50. Describe how stress affects immune responses.

22.1 Organs and Structures of the Respiratory System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- List the structures that make up the respiratory system
- Describe how the respiratory system processes oxygen and CO_2
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing (Figure 22.2).

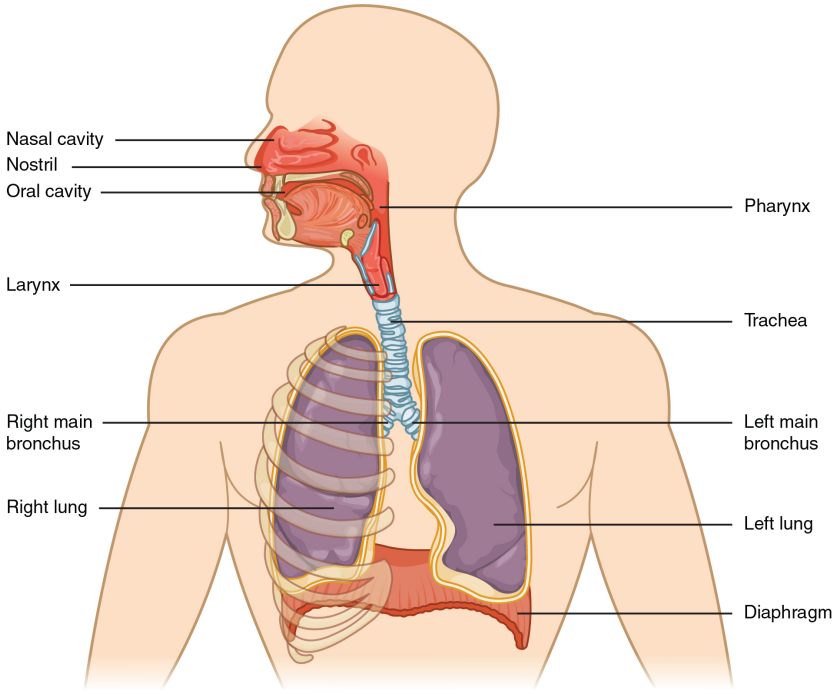


FIGURE 22.2 Major Respiratory Structures The major respiratory structures span the nasal cavity to the diaphragm.

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The **external nose** consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions (Figure 22.3). The **root** is the region of the nose located between the eyebrows. The **bridge** is the part of the nose that connects the root to the rest of the nose. The **dorsum nasi** is the length of the nose. The **apex** is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An **ala** is a cartilaginous structure that forms the lateral side of each **naris** (plural = nares), or nostril opening. The **philtrum** is the concave surface that connects the apex of the nose to the upper lip.

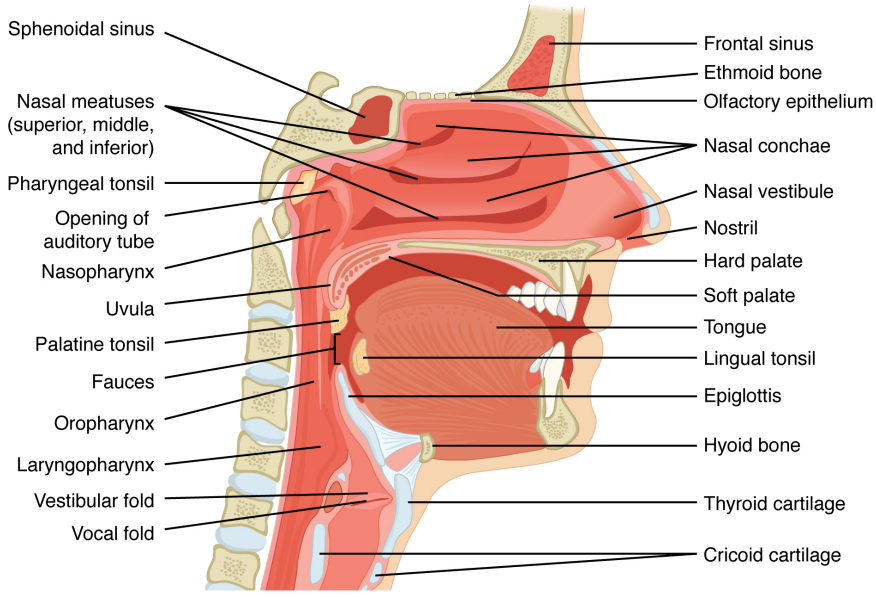


FIGURE 22.4 Upper Airway

Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each **paranasal sinus** is named for its associated bone: frontal sinus, maxillary sinus, sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

The conchae, meatuses, and paranasal sinuses are lined by **respiratory epithelium** composed of pseudostratified ciliated columnar epithelium (Figure 22.5). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

The **nasopharynx** is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A **pharyngeal tonsil**, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory (Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

The **oropharynx** is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The **fauces** is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A **palatine tonsil** is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The **lingual tonsil** is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

The **laryngopharynx** is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

Larynx

The **larynx** is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs (Figure 22.7). The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The **thyroid cartilage** is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the **laryngeal prominence**, or “Adam’s apple,” which tends to be more prominent in males. The thick **cricoid cartilage** forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

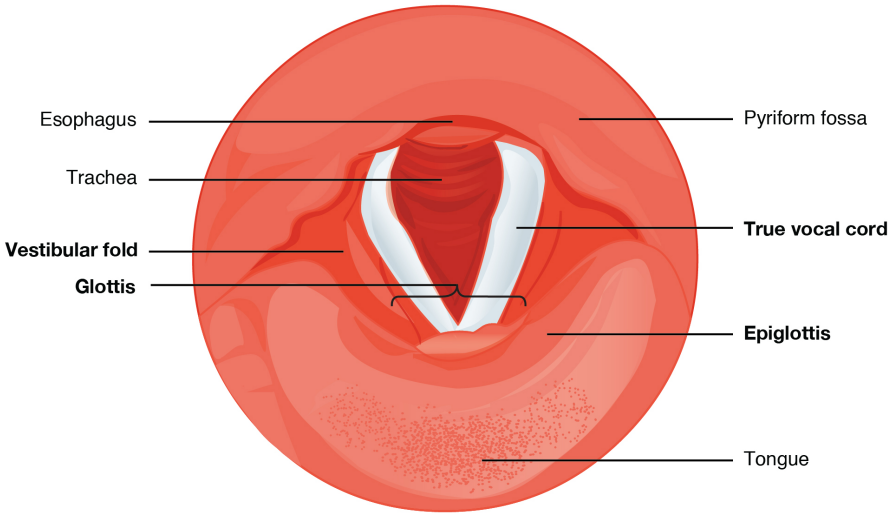


FIGURE 22.8 Vocal Cords The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

Trachea

The trachea (windpipe) extends from the larynx toward the lungs (Figure 22.9**a**). The **trachea** is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

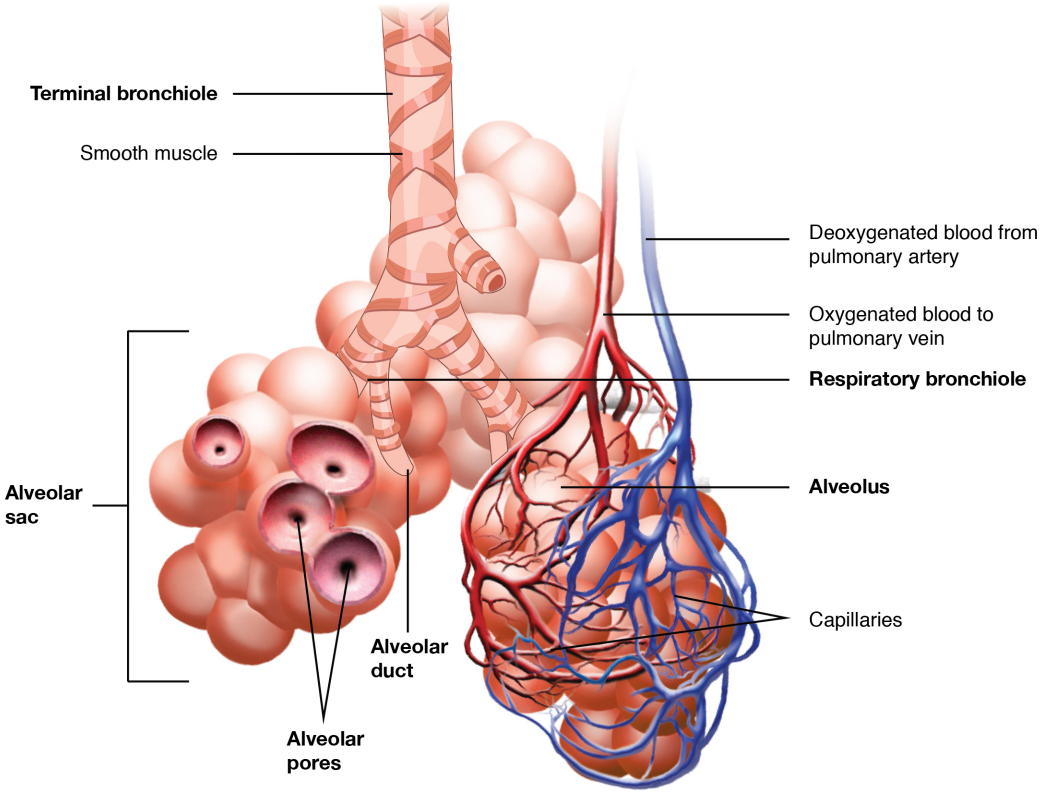


FIGURE 22.10 Respiratory Zone Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

Alveoli

An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 µm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung (Figure 22.11).

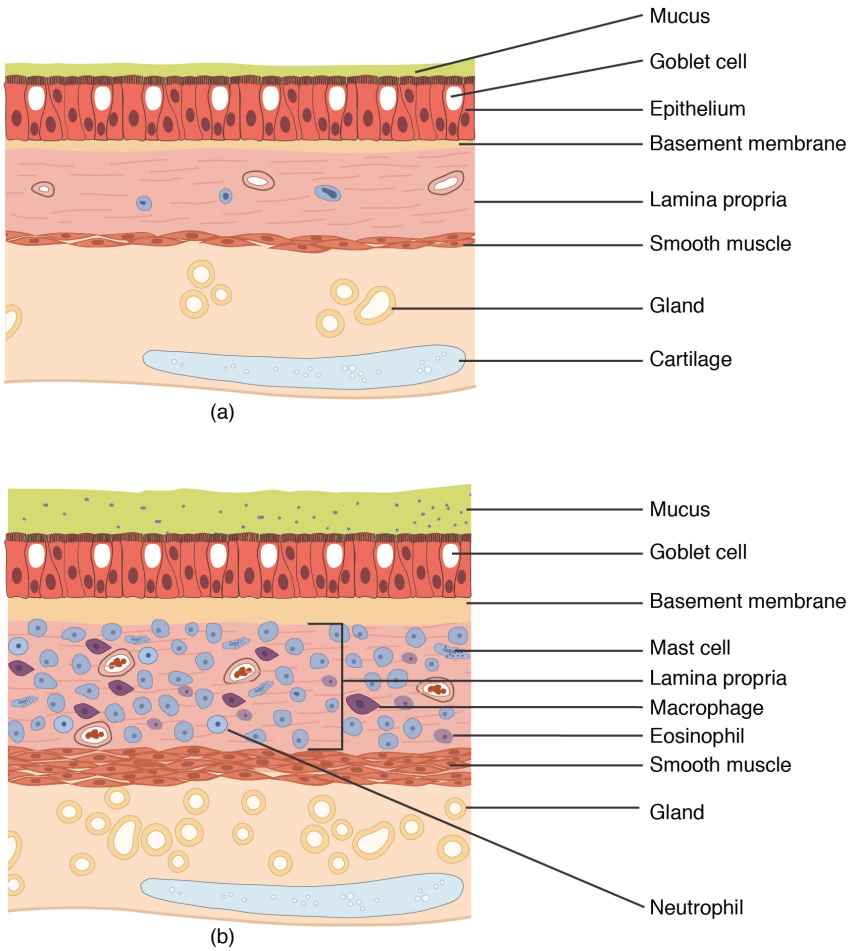


FIGURE 22.12 **Normal and Bronchial Asthma Tissues** (a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer.

In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/asthma) to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

throughout the body. In addition, innervation by the both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the **hilum**.

Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction**, whereas the sympathetic nervous system stimulates **bronchodilation**. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The **pulmonary plexus** is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs, and extends into and lines the lung fissures (Figure 22.14). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.

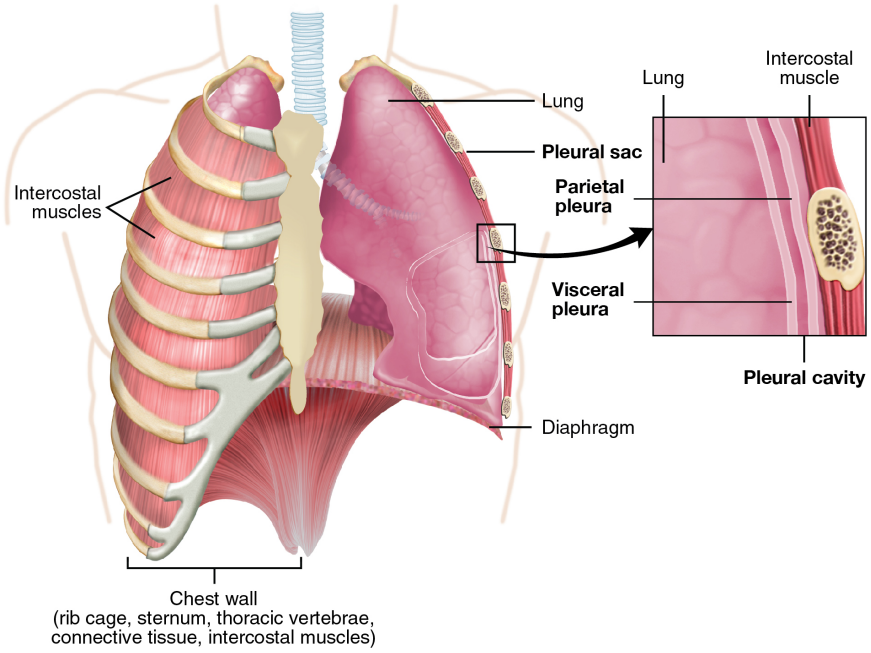


FIGURE 22.14 Parietal and Visceral Pleurae of the Lungs

ability to breathe—to have air enter the lungs during inspiration and air leave the lungs during expiration—is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

Pressure Relationships

Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules in a one-liter container (Figure 22.15). In this case, the force exerted by the movement of the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related ($P = k/V$). Therefore, the pressure in the one-liter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

$$P_1 V_1 = P_2 V_2$$

In this formula, P_1 represents the initial pressure and V_1 represents the initial volume, whereas the final pressure and volume are represented by P_2 and V_2, respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).

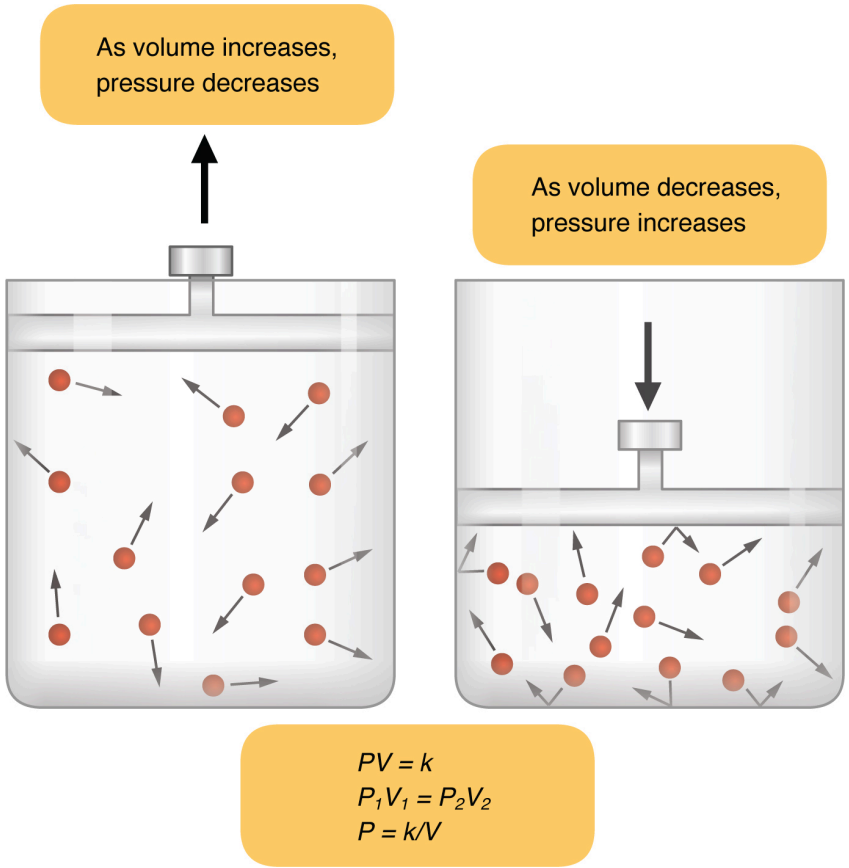


FIGURE 22.15 Boyle's Law In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and intrapleural. **Atmospheric pressure** is the amount of force that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore,

relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

$$F = \Delta P/R$$

As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

Thoracic wall compliance is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. **Inspiration** is the process that causes air to enter the lungs, and **expiration** is the process that causes air to leave the lungs (Figure 22.17). A **respiratory cycle** is one sequence of inspiration and expiration. In general, two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.

dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health (Figure 22.19).

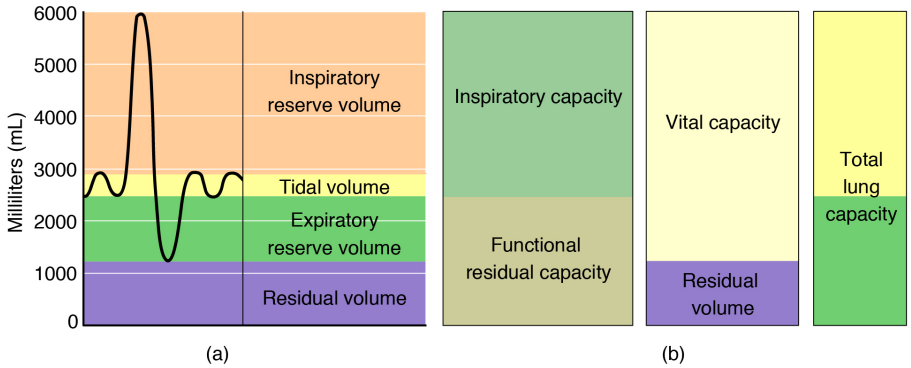


FIGURE 22.18 Respiratory Volumes and Capacities These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

Pulmonary function test	Instrument	Measures	Function
Spirometry	Spirometer	Forced vital capacity (FVC)	Volume of air that is exhaled after maximum inhalation
		Forced expiratory volume (FEV)	Volume of air exhaled during one forced breath
		Forced expiratory flow, 25–75 percent	Air flow in the middle of exhalation
		Peak expiratory flow (PEF)	Rate of exhalation
		Maximum voluntary ventilation (MVV)	Volume of air that can be inspired and expired in 1 minute
		Slow vital capacity (SVC)	Volume of air that can be slowly exhaled after inhaling past the tidal volume
		Total lung capacity (TLC)	Volume of air in the lungs after maximum inhalation
		Functional residual capacity (FRC)	Volume of air left in the lungs after normal expiration
		Residual volume (RV)	Volume of air in the lungs after maximum exhalation
		Total lung capacity (TLC)	Maximum volume of air that the lungs can hold
		Expiratory reserve volume (ERV)	The volume of air that can be exhaled beyond normal exhalation
Gas diffusion	Blood gas analyzer	Arterial blood gases	Concentration of oxygen and carbon dioxide in the blood

FIGURE 22.19 Pulmonary Function Testing

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example, **total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for males, and about 4200 mL for females. **Vital capacity (VC)** is the amount of air a person can move into or out of their lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)** is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume (see Figure 22.18).

INTERACTIVE LINK

Watch this video (http://openstax.org/l/spirometers) to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group (Figure 22.20).

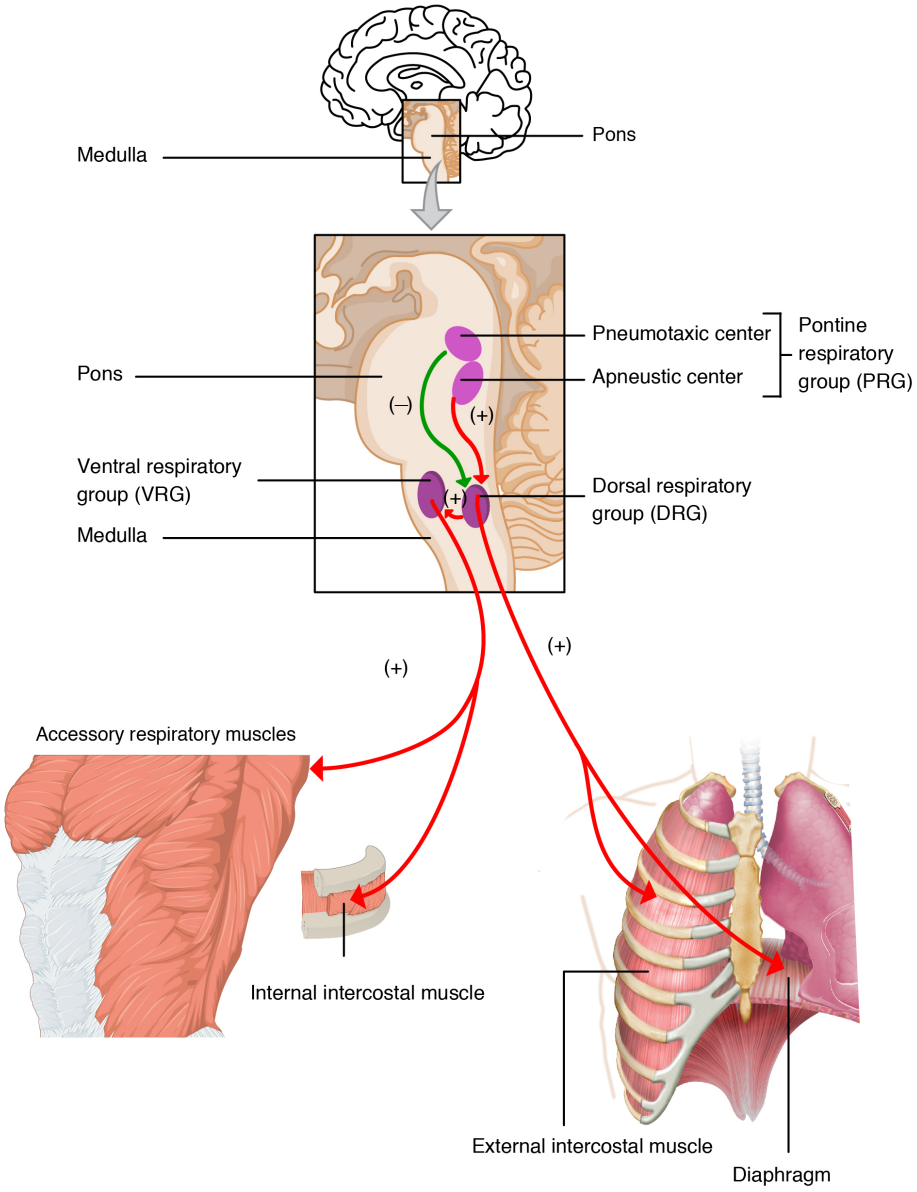


FIGURE 22.20 **Respiratory Centers of the Brain**

The medulla oblongata contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and pneumotaxic centers. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The **pneumotaxic center** is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway. Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow.

In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.

A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea–promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.

22.4 Gas Exchange

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare the composition of atmospheric air and alveolar air
- Describe the mechanisms that drive gas exchange
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Describe the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

Gas Laws and Air Composition

Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure (Table 22.2). **Partial pressure** (P_x) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen (Figure 22.21). **Total pressure** is the sum of all the partial pressures of a gaseous mixture. **Dalton's law** describes the behavior of nonreactive gases in a

gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

Composition and Partial Pressures of Alveolar Air

Gas	Percent of total composition	Partial pressure (mm Hg)
Nitrogen (N_2)	74.9	569
Oxygen (O_2)	13.7	104
Water (H_2O)	6.2	40
Carbon dioxide (CO_2)	5.2	47
Total composition/total alveolar pressure	100%	760.0

TABLE 22.3

Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of oxygenated blood in pulmonary veins is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serves the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

Gas Exchange

Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the

that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure of carbon dioxide has returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

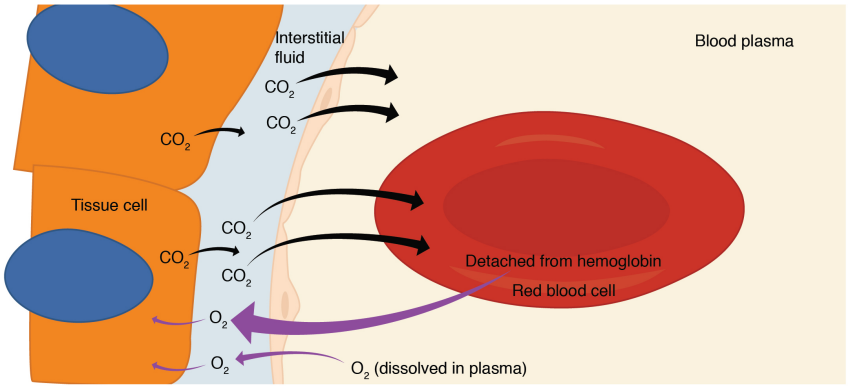


FIGURE 22.23 **Internal Respiration** Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

Everyday Connection

Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically for one patient, and the staff tending to the patient observes the patient from outside of the chamber (Figure 22.24). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.

total amount. The majority of oxygen molecules are carried from the lungs to the body's tissues by a specialized transport system, which relies on the erythrocyte—the red blood cell. Erythrocytes contain a metalloprotein, hemoglobin, which serves to bind oxygen molecules to the erythrocyte (Figure 22.25). Heme is the portion of hemoglobin that contains iron, and it is heme that binds oxygen. Each hemoglobin molecule contains four iron-containing heme molecules, and because of this, one hemoglobin molecule is capable of carrying up to four molecules of oxygen. As oxygen diffuses across the respiratory membrane from the alveolus to the capillary, it also diffuses into the red blood cell and is bound by hemoglobin. The following reversible chemical reaction describes the production of the final product, **oxyhemoglobin** (HbO_2), which is formed when oxygen binds to hemoglobin. Oxyhemoglobin is a bright red-colored molecule that contributes to the bright red color of oxygenated blood.

$$Hb + O_2 \leftrightarrow HbO_2$$

In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to and dissociates from oxygen, which will be discussed in the subsequent sections.

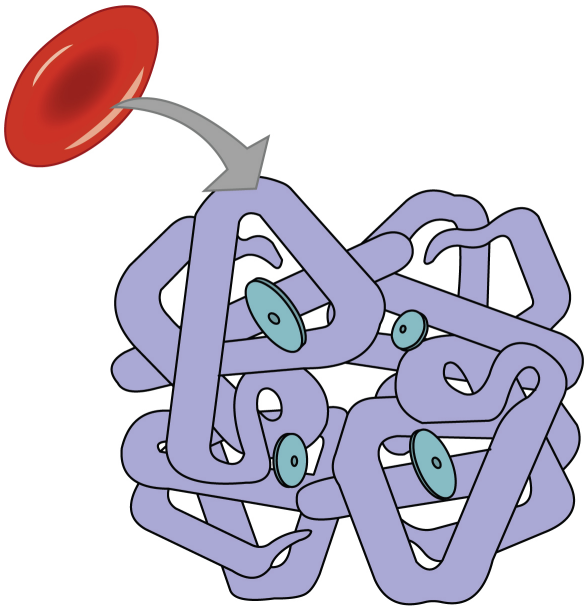


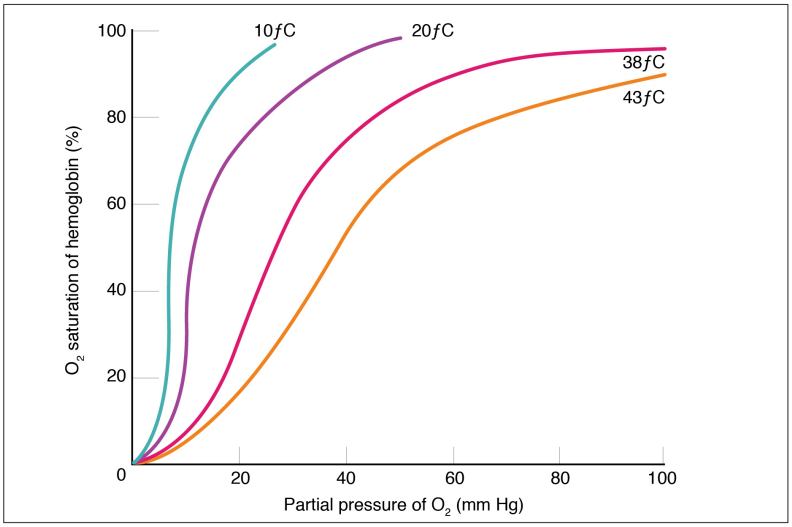
FIGURE 22.25 Erythrocyte and Hemoglobin Hemoglobin consists of four subunits, each of which contains one molecule of iron.

Function of Hemoglobin

Hemoglobin is composed of subunits, a protein structure that is referred to as a quaternary structure. Each of the four subunits that make up hemoglobin is arranged in a ring-like fashion, with an iron atom covalently bound to the heme in the center of each subunit. Binding of the first oxygen molecule causes a conformational change in hemoglobin that allows the second molecule of oxygen to bind more readily. As each molecule of oxygen is bound, it further facilitates the binding of the next molecule, until all four heme sites are occupied by oxygen. The opposite occurs as well: After the first oxygen molecule dissociates and is "dropped off" at the tissues, the next oxygen molecule dissociates more readily. When all four heme sites are occupied, the hemoglobin is said to be saturated. When one to three heme sites are occupied, the hemoglobin is said to be partially saturated. Therefore, when considering the blood as a whole, the percent of the available heme units that are bound to oxygen at a given time is called hemoglobin saturation. Hemoglobin saturation of 100 percent means that every heme unit in all of the erythrocytes of the body is bound to oxygen. In a healthy individual with normal hemoglobin levels, hemoglobin saturation generally ranges from 95 percent to 99 percent.

Oxygen Dissociation from Hemoglobin

Partial pressure is an important aspect of the binding of oxygen to and disassociation from heme. An **oxygen–hemoglobin dissociation curve** is a graph that describes the relationship of partial pressure to the binding of oxygen to heme and its subsequent dissociation from heme (Figure 22.26). Remember that gases travel from an area of higher partial pressure to an area of lower partial pressure. In addition, the affinity of an oxygen molecule for heme increases as more oxygen molecules are bound. Therefore, in the oxygen–hemoglobin saturation curve, as the



(c) Effect of temperature

FIGURE 22.26 Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature These three graphs show (a) the relationship between the partial pressure of oxygen and hemoglobin saturation, (b) the effect of pH on the oxygen–hemoglobin dissociation curve, and (c) the effect of temperature on the oxygen–hemoglobin dissociation curve.

The mechanisms behind the oxygen–hemoglobin saturation/dissociation curve also serve as automatic control mechanisms that regulate how much oxygen is delivered to different tissues throughout the body. This is important because some tissues have a higher metabolic rate than others. Highly active tissues, such as muscle, rapidly use oxygen to produce ATP, lowering the partial pressure of oxygen in the tissue to about 20 mm Hg. The partial pressure of oxygen inside capillaries is about 100 mm Hg, so the difference between the two becomes quite high, about 80 mm Hg. As a result, a greater number of oxygen molecules dissociate from hemoglobin and enter the tissues. The reverse is true of tissues, such as adipose (body fat), which have lower metabolic rates. Because less oxygen is used by these cells, the partial pressure of oxygen within such tissues remains relatively high, resulting in fewer oxygen molecules dissociating from hemoglobin and entering the tissue interstitial fluid. Although venous blood is said to be deoxygenated, some oxygen is still bound to hemoglobin in its red blood cells. This provides an oxygen reserve that can be used when tissues suddenly demand more oxygen.

Factors other than partial pressure also affect the oxygen–hemoglobin saturation/dissociation curve. For example, a higher temperature promotes hemoglobin and oxygen to dissociate faster, whereas a lower temperature inhibits dissociation (see Figure 22.26**, middle**). However, the human body tightly regulates temperature, so this factor may not affect gas exchange throughout the body. The exception to this is in highly active tissues, which may release a larger amount of energy than is given off as heat. As a result, oxygen readily dissociates from hemoglobin, which is a mechanism that helps to provide active tissues with more oxygen.

Certain hormones, such as androgens, epinephrine, thyroid hormones, and growth hormone, can affect the oxygen–hemoglobin saturation/disassociation curve by stimulating the production of a compound called 2,3-bisphosphoglycerate (BPG) by erythrocytes. BPG is a byproduct of glycolysis. Because erythrocytes do not contain mitochondria, glycolysis is the sole method by which these cells produce ATP. BPG promotes the disassociation of oxygen from hemoglobin. Therefore, the greater the concentration of BPG, the more readily oxygen dissociates from hemoglobin, despite its partial pressure.

The pH of the blood is another factor that influences the oxygen–hemoglobin saturation/dissociation curve (see Figure 22.26). The **Bohr effect** is a phenomenon that arises from the relationship between pH and oxygen's affinity for hemoglobin: A lower, more acidic pH promotes oxygen dissociation from hemoglobin. In contrast, a higher, or more basic, pH inhibits oxygen dissociation from hemoglobin. The greater the amount of carbon dioxide in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream.

Hemoglobin of the Fetus

The fetus has its own circulation with its own erythrocytes; however, it is dependent on the pregnant person for

Dissolved Carbon Dioxide

Although carbon dioxide is not considered to be highly soluble in blood, a small fraction—about 7 to 10 percent—of the carbon dioxide that diffuses into the blood from the tissues dissolves in plasma. The dissolved carbon dioxide then travels in the bloodstream and when the blood reaches the pulmonary capillaries, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is then exhaled during pulmonary ventilation.

Bicarbonate Buffer

A large fraction—about 70 percent—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into the capillaries, and subsequently into red blood cells. **Carbonic anhydrase (CA)** causes carbon dioxide and water to form carbonic acid (H_2CO_3), which dissociates into two ions: bicarbonate (HCO_3^-) and hydrogen (H^+). The following formula depicts this reaction:

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3\_$$

Bicarbonate tends to build up in the erythrocytes, so that there is a greater concentration of bicarbonate in the erythrocytes than in the surrounding blood plasma. As a result, some of the bicarbonate will leave the erythrocytes and move down its concentration gradient into the plasma in exchange for chloride (Cl^-) ions. This phenomenon is referred to as the **chloride shift** and occurs because by exchanging one negative ion for another negative ion, neither the electrical charge of the erythrocytes nor that of the blood is altered.

At the pulmonary capillaries, the chemical reaction that produced bicarbonate (shown above) is reversed, and carbon dioxide and water are the products. Much of the bicarbonate in the plasma re-enters the erythrocytes in exchange for chloride ions. Hydrogen ions and bicarbonate ions join to form carbonic acid, which is converted into carbon dioxide and water by carbonic anhydrase. Carbon dioxide diffuses out of the erythrocytes and into the plasma, where it can further diffuse across the respiratory membrane into the alveoli to be exhaled during pulmonary ventilation.

Carbaminohemoglobin

About 20 percent of carbon dioxide is bound by hemoglobin and is transported to the lungs. Carbon dioxide does not bind to iron as oxygen does; instead, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form **carbaminohemoglobin**, which forms when hemoglobin and carbon dioxide bind. When hemoglobin is not transporting oxygen, it tends to have a bluish-purple tone to it, creating the darker maroon color typical of deoxygenated blood. The following formula depicts this reversible reaction:

$$CO_2 + Hb \leftrightarrow HbCO_2$$

Similar to the transport of oxygen by heme, the binding and dissociation of carbon dioxide to and from hemoglobin is dependent on the partial pressure of carbon dioxide. Because carbon dioxide is released from the lungs, blood that leaves the lungs and reaches body tissues has a lower partial pressure of carbon dioxide than is found in the tissues. As a result, carbon dioxide leaves the tissues because of its higher partial pressure, enters the blood, and then moves into red blood cells, binding to hemoglobin. In contrast, in the pulmonary capillaries, the partial pressure of carbon dioxide is high compared to within the alveoli. As a result, carbon dioxide dissociates readily from hemoglobin and diffuses across the respiratory membrane into the air.

In addition to the partial pressure of carbon dioxide, the oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood also influence the affinity of hemoglobin for carbon dioxide. The **Haldane effect** is a phenomenon that arises from the relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide. Hemoglobin that is saturated with oxygen does not readily bind carbon dioxide. However, when oxygen is not bound to heme and the partial pressure of oxygen is low, hemoglobin readily binds to carbon dioxide.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/oxyblood) to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Partial Pressure of Oxygen at Different Altitudes

Example location	Altitude (feet above sea level)	Atmospheric pressure (mm Hg)	Partial pressure of oxygen (mm Hg)
New York City, New York	0	760	159
Boulder, Colorado	5000	632	133
Aspen, Colorado	8000	565	118
Pike's Peak, Colorado	14,000	447	94
Denali (Mt. McKinley), Alaska	20,000	350	73
Mt. Everest, Tibet	29,000	260	54

TABLE 22.4

As you recall, partial pressure is extremely important in determining how much gas can cross the respiratory membrane and enter the blood of the pulmonary capillaries. A lower partial pressure of oxygen means that there is a smaller difference in partial pressures between the alveoli and the blood, so less oxygen crosses the respiratory membrane. As a result, fewer oxygen molecules are bound by hemoglobin. Despite this, the tissues of the body still receive a sufficient amount of oxygen during rest at high altitudes. This is due to two major mechanisms. First, the number of oxygen molecules that enter the tissue from the blood is nearly equal between sea level and high altitudes. At sea level, hemoglobin saturation is higher, but only a quarter of the oxygen molecules are actually released into the tissue. At high altitudes, a greater proportion of molecules of oxygen are released into the tissues. Secondly, at high altitudes, a greater amount of BPG is produced by erythrocytes, which enhances the dissociation of oxygen from hemoglobin. Physical exertion, such as skiing or hiking, can lead to altitude sickness due to the low amount of oxygen reserves in the blood at high altitudes. At sea level, there is a large amount of oxygen reserve in venous blood (even though venous blood is thought of as "deoxygenated") from which the muscles can draw during physical exertion. Because the oxygen saturation is much lower at higher altitudes, this venous reserve is small, resulting in pathological symptoms of low blood oxygen levels. You may have heard that it is important to drink more water when traveling at higher altitudes than you are accustomed to. This is because your body will increase micturition (urination) at high altitudes to counteract the effects of lower oxygen levels. By removing fluids, blood plasma levels drop but not the total number of erythrocytes. In this way, the overall concentration of erythrocytes in the blood increases, which helps tissues obtain the oxygen they need.

Acute mountain sickness (AMS), or altitude sickness, is a condition that results from acute exposure to high altitudes due to a low partial pressure of oxygen at high altitudes. AMS typically can occur at 2400 meters (8000 feet) above sea level. AMS is a result of low blood oxygen levels, as the body has acute difficulty adjusting to the low partial pressure of oxygen. In serious cases, AMS can cause pulmonary or cerebral edema. Symptoms of AMS include nausea, vomiting, fatigue, lightheadedness, drowsiness, feeling disoriented, increased pulse, and nosebleeds. The only treatment for AMS is descending to a lower altitude; however, pharmacologic treatments and supplemental oxygen can improve symptoms. AMS can be prevented by slowly ascending to the desired altitude, allowing the body to acclimate, as well as maintaining proper hydration.

Acclimatization

Especially in situations where the ascent occurs too quickly, traveling to areas of high altitude can cause AMS. **Acclimatization** is the process of adjustment that the respiratory system makes due to chronic exposure to a high altitude. Over a period of time, the body adjusts to accommodate the lower partial pressure of oxygen. The low partial pressure of oxygen at high altitudes results in a lower oxygen saturation level of hemoglobin in the blood. In

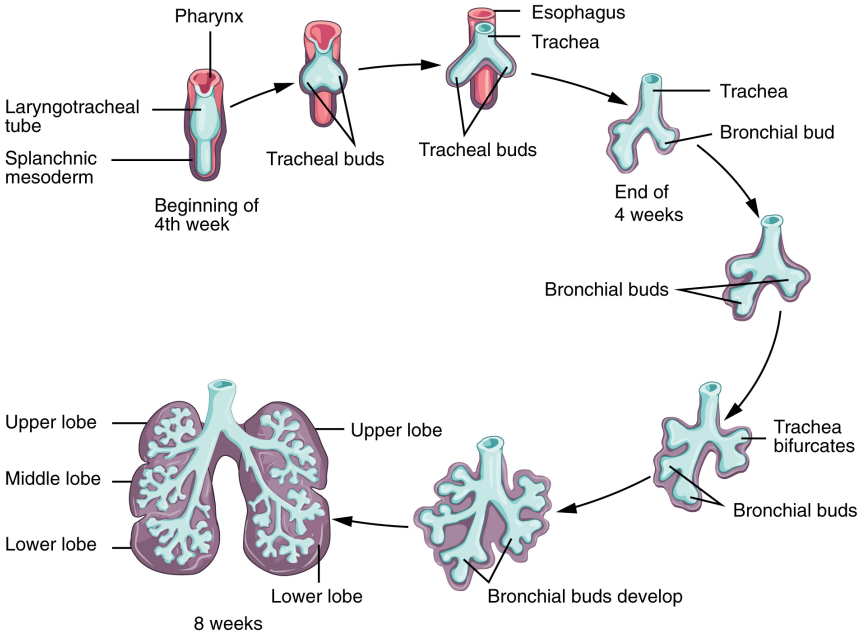


FIGURE 22.29 **Development of the Lower Respiratory System**

Weeks 7–16

Bronchial buds continue to branch as development progresses until all of the segmental bronchi have been formed. Beginning around week 13, the lumens of the bronchi begin to expand in diameter. By week 16, respiratory bronchioles form. The fetus now has all major lung structures involved in the airway.

Weeks 16–24

Once the respiratory bronchioles form, further development includes extensive vascularization, or the development of the blood vessels, as well as the formation of alveolar ducts and alveolar precursors. At about week 19, the respiratory bronchioles have formed. In addition, cells lining the respiratory structures begin to differentiate to form type I and type II pneumocytes. Once type II cells have differentiated, they begin to secrete small amounts of pulmonary surfactant. Around week 20, fetal breathing movements may begin.

Weeks 24–Term

Major growth and maturation of the respiratory system occurs from week 24 until term. More alveolar precursors develop, and larger amounts of pulmonary surfactant are produced. Surfactant levels are not generally adequate to create effective lung compliance until about the eighth month of pregnancy. The respiratory system continues to expand, and the surfaces that will form the respiratory membrane develop further. At this point, pulmonary capillaries have formed and continue to expand, creating a large surface area for gas exchange. The major milestone of respiratory development occurs at around week 28, when sufficient alveolar precursors have matured so that a baby born prematurely at this time can usually breathe on its own. However, alveoli continue to develop and mature into childhood. A full complement of functional alveoli does not appear until around 8 years of age.

Fetal “Breathing”

Although the function of fetal breathing movements is not entirely clear, they can be observed starting at 20–21 weeks of development. Fetal breathing movements involve muscle contractions that cause the inhalation of amniotic fluid and exhalation of the same fluid, with pulmonary surfactant and mucus. Fetal breathing movements are not continuous and may include periods of frequent movements and periods of no movements. Maternal factors can influence the frequency of breathing movements. For example, high blood glucose levels, called hyperglycemia, can boost the number of breathing movements. Conversely, low blood glucose levels, called hypoglycemia, can reduce the number of fetal breathing movements. Tobacco use is also known to lower fetal breathing rates. Fetal breathing may help tone the muscles in preparation for breathing movements once the fetus is born. It may also help the alveoli to form and mature. Fetal breathing movements are considered a sign of robust health.

Key Terms

acclimatization process of adjustment that the respiratory system makes due to chronic exposure to high altitudes

acute mountain sickness (AMS) condition that occurs a result of acute exposure to high altitude due to a low partial pressure of oxygen

ala (plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

alar cartilage cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

alveolar dead space air space within alveoli that are unable to participate in gas exchange

alveolar duct small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage immune system cell of the alveolus that removes debris and pathogens

alveolar pore opening that allows airflow between neighboring alveoli

alveolar sac cluster of alveoli

alveolus small, grape-like sac that performs gas exchange in the lungs

anatomical dead space air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange

apex tip of the external nose

apneustic center network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration

atmospheric pressure amount of force that is exerted by gases in the air surrounding any given surface

Bohr effect relationship between blood pH and oxygen dissociation from hemoglobin

Boyle's law relationship between volume and pressure as described by the formula: $P_1V_1 = P_2V_2$

bridge portion of the external nose that lies in the area of the nasal bones

bronchial bud structure in the developing embryo that forms when the laryngotracheal bud extends and branches to form two bulbous structures

bronchial tree collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bronchiole branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchoconstriction decrease in the size of the bronchiole due to relaxation of the muscular wall

bronchodilation increase in the size of the bronchiole due to contraction of the muscular wall

bronchus tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

carbaminohemoglobin bound form of hemoglobin and carbon dioxide

carbonic anhydrase (CA) enzyme that catalyzes the reaction that causes carbon dioxide and water to form carbonic acid

cardiac notch indentation on the surface of the left lung that allows space for the heart

central chemoreceptor one of the specialized receptors that are located in the brain that sense changes in hydrogen ion, oxygen, or carbon dioxide concentrations in the brain

chloride shift facilitated diffusion that exchanges bicarbonate (HCO_3^-) with chloride (Cl^-) ions

conducting zone region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

cricoid cartilage portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

Dalton's law statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

dorsal respiratory group (DRG) region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration

dorsum nasi intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

epiglottis leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

expiration (also, exhalation) process that causes the air to leave the lungs

expiratory reserve volume (ERV) amount of air that can be forcefully exhaled after a normal tidal exhalation

external nose region of the nose that is easily visible to others

external respiration gas exchange that occurs in the alveoli

fauces portion of the posterior oral cavity that connects the oral cavity to the oropharynx

fibroelastic membrane specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

forced breathing (also, hyperpnea) mode of

the esophagus and trachea

philtrum concave surface of the face that connects the apex of the nose to the top lip

pleural cavity space between the visceral and parietal pleurae

pleural fluid substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pneumotaxic center network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing

pulmonary artery artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

pulmonary plexus network of autonomic nervous system fibers found near the hilum of the lung

pulmonary surfactant substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

pulmonary ventilation exchange of gases between the lungs and the atmosphere; breathing

quiet breathing (also, eupnea) mode of breathing that occurs at rest and does not require the cognitive thought of the individual

residual volume (RV) amount of air that remains in the lungs after maximum exhalation

respiratory bronchiole specific type of bronchiole that leads to alveolar sacs

respiratory cycle one sequence of inspiration and expiration

respiratory epithelium ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory rate total number of breaths taken each minute

respiratory volume varying amounts of air within the lung at a given time

respiratory zone includes structures of the respiratory system that are directly involved in gas exchange

root region of the external nose between the eyebrows

thoracic wall compliance ability of the thoracic wall to stretch while under pressure

thyroid cartilage largest piece of cartilage that makes up the larynx and consists of two lamine

tidal volume (TV) amount of air that normally enters the lungs during quiet breathing

total dead space sum of the anatomical dead space and alveolar dead space

total lung capacity (TLC) total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV

total pressure sum of all the partial pressures of a gaseous mixture

trachea tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

trachealis muscle smooth muscle located in the fibroelastic membrane of the trachea

transpulmonary pressure pressure difference between the intrapleural and intra-alveolar pressures

true vocal cord one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

type I alveolar cell squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

ventilation movement of air into and out of the lungs; consists of inspiration and expiration

ventral respiratory group (VRG) region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration

vestibular fold part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

visceral pleura innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

vital capacity (VC) sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange

Chapter Review

22.1 Organs and Structures of the Respiratory System

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and meatuses that

volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume. Respiratory capacity is the combination of two or more volumes. Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

22.4 Gas Exchange

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

22.5 Transport of Gases

Oxygen is primarily transported through the blood by erythrocytes. These cells contain a metalloprotein called hemoglobin, which is composed of four subunits with a ring-like structure. Each subunit contains one atom of iron bound to a molecule of heme. Heme binds oxygen so that each hemoglobin molecule can bind up to four oxygen molecules. When all of the heme units in the blood are bound to oxygen, hemoglobin is considered to be saturated. Hemoglobin is partially saturated when only some heme units are bound to oxygen. An oxygen–hemoglobin saturation/dissociation curve is a common way to depict the relationship of how easily oxygen binds to or dissociates from hemoglobin as a function of the partial pressure of oxygen. As the partial pressure of oxygen increases, the more readily hemoglobin binds to oxygen. At the same time, once one molecule of oxygen is bound by hemoglobin, additional oxygen molecules more readily bind to hemoglobin. Other factors such as temperature, pH, the partial pressure of carbon dioxide, and the concentration of 2,3-bisphosphoglycerate can enhance or inhibit the binding of hemoglobin and oxygen as well. Fetal hemoglobin has a different structure than adult hemoglobin, which results in fetal hemoglobin having a greater affinity for oxygen than adult hemoglobin.

Carbon dioxide is transported in blood by three different mechanisms: as dissolved carbon dioxide, as bicarbonate, or as carbaminohemoglobin. A small portion of carbon dioxide remains. The largest amount of transported carbon dioxide is as bicarbonate, formed in erythrocytes. For this conversion, carbon dioxide is combined with water with the aid of an enzyme called carbonic anhydrase. This combination forms carbonic acid, which spontaneously dissociates into bicarbonate and hydrogen ions. As bicarbonate builds up in erythrocytes, it is moved across the membrane into the plasma in exchange for chloride ions by a mechanism called the chloride shift. At the pulmonary capillaries, bicarbonate re-enters erythrocytes in exchange for chloride ions, and the reaction with carbonic anhydrase is reversed, recreating carbon dioxide and water. Carbon dioxide

Review Questions

4. Which of the following anatomical structures is *not* part of the conducting zone?
a. pharynx
b. nasal cavity
c. alveoli
d. bronchi

5. What is the function of the conchae in the nasal cavity?
a. increase surface area
b. exchange gases
c. maintain surface tension
d. maintain air pressure

6. The fauces connects which of the following structures to the oropharynx?
a. nasopharynx
b. laryngopharynx
c. nasal cavity
d. oral cavity

7. Which of the following are structural features of the trachea?
a. C-shaped cartilage
b. smooth muscle fibers
c. cilia
d. all of the above

8. Which of the following structures is *not* part of the bronchial tree?
a. alveoli
b. bronchi
c. terminal bronchioles
d. respiratory bronchioles

9. What is the role of alveolar macrophages?
a. to secrete pulmonary surfactant
b. to secrete antimicrobial proteins
c. to remove pathogens and debris
d. to facilitate gas exchange

10. Which of the following structures separates the lung into lobes?
a. mediastinum
b. fissure
c. root
d. pleura

11. A section of the lung that receives its own tertiary bronchus is called the _____.
a. bronchopulmonary segment
b. pulmonary lobule
c. interpulmonary segment
d. respiratory segment

12. The _____ circulation picks up oxygen for cellular use and drops off carbon dioxide for removal from the body.
a. pulmonary
b. interlobular
c. respiratory
d. bronchial

13. The pleura that surrounds the lungs consists of two layers, the _____.
a. visceral and parietal pleurae.
b. mediastinum and parietal pleurae.
c. visceral and mediastinum pleurae.
d. none of the above

14. Which of the following processes does atmospheric pressure play a role in?
a. pulmonary ventilation
b. production of pulmonary surfactant
c. resistance
d. surface tension

15. A decrease in volume leads to a(n) _____ pressure.
a. decrease in
b. equalization of
c. increase in
d. zero

16. The pressure difference between the intra-alveolar and intrapleural pressures is called _____.
a. atmospheric pressure
b. pulmonary pressure
c. negative pressure
d. transpulmonary pressure

17. Gas flow decreases as _____ increases.
a. resistance
b. pressure
c. airway diameter
d. friction

18. Contraction of the external intercostal muscles causes which of the following to occur?
a. The diaphragm moves downward.
b. The rib cage is compressed.
c. The thoracic cavity volume decreases.
d. The ribs and sternum move upward.

33. If a baby is born prematurely before type II cells produce sufficient pulmonary surfactant, which of the following might you expect?
   a. difficulty expressing fluid
   b. difficulty inflating the lungs
   c. difficulty with pulmonary capillary flow
   d. no difficulty as type I cells can provide enough surfactant for normal breathing

34. When do fetal breathing movements begin?
   a. around week 20
   b. around week 37
   c. around week 16
   d. after birth

35. What happens to the fluid that remains in the lungs after birth?
   a. It reduces the surface tension of the alveoli.
   b. It is expelled shortly after birth.
   c. It is absorbed shortly after birth.
   d. It lubricates the pleurae.

Critical Thinking Questions

36. Describe the three regions of the pharynx and their functions.

37. If a person sustains an injury to the epiglottis, what would be the physiological result?

38. Compare and contrast the conducting and respiratory zones.

39. Compare and contrast the right and left lungs.

40. Why are the pleurae not damaged during normal breathing?

41. Describe what is meant by the term “lung compliance.”

42. Outline the steps involved in quiet breathing.

43. What is respiratory rate and how is it controlled?

44. Compare and contrast Dalton’s law and Henry’s law.

45. A smoker develops damage to several alveoli that then can no longer function. How does this affect gas exchange?

46. Compare and contrast adult hemoglobin and fetal hemoglobin.

47. Describe the relationship between the partial pressure of oxygen and the binding of oxygen to hemoglobin.

48. Describe three ways in which carbon dioxide can be transported.

49. Describe the neural factors involved in increasing ventilation during exercise.

50. What is the major mechanism that results in acclimatization?

51. During what timeframe does a fetus have enough mature structures to breathe on its own if born prematurely? Describe the other structures that develop during this phase.

52. Describe fetal breathing movements and their purpose.

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process (Figure 23.2).

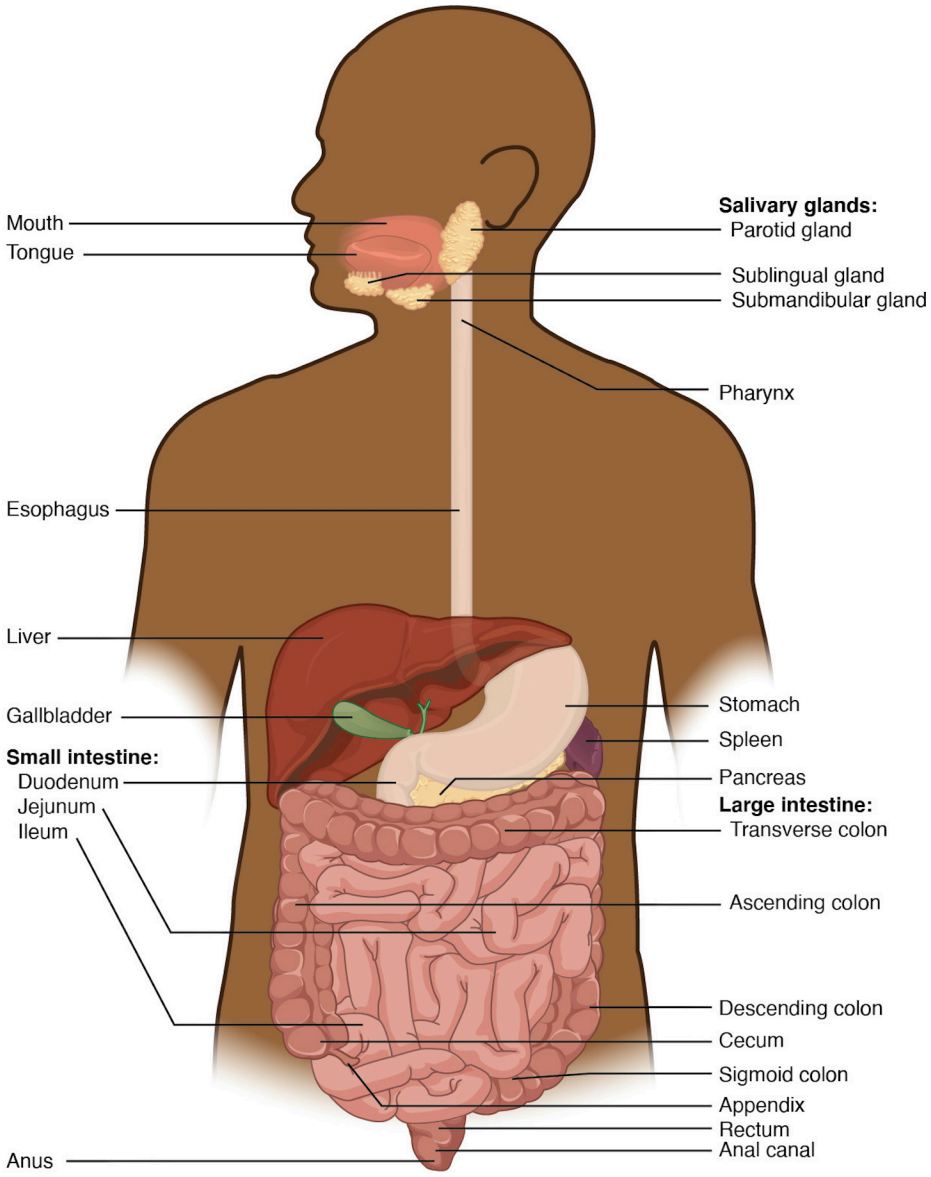


FIGURE 23.2 Components of the Digestive System All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. Table 23.1 gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (see Figure 23.3).

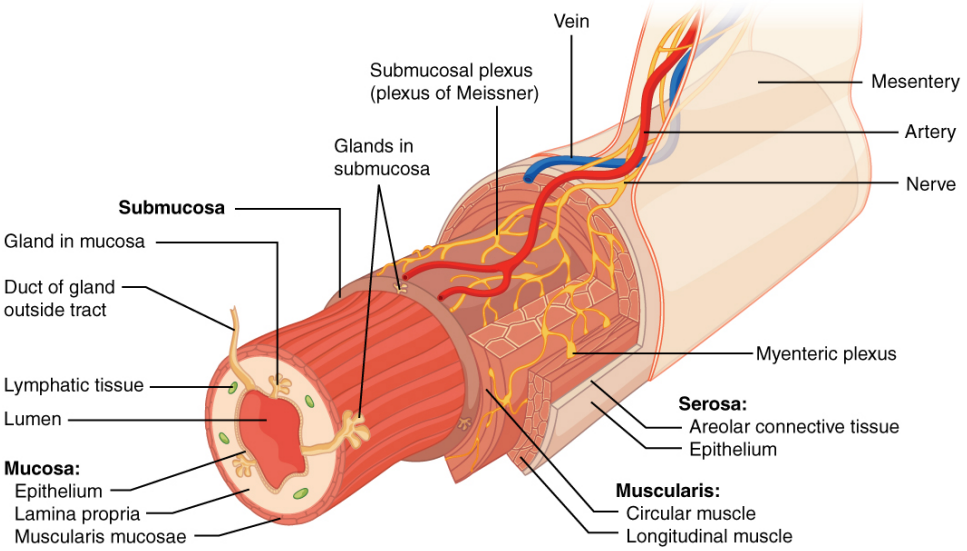


FIGURE 23.3 Layers of the Alimentary Canal The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.

The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosae (not to be confused with the muscularis layer, described below).

Epithelium—In the mouth, pharynx, esophagus, and anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer's patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosae—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscularis** (also called the muscularis externa). The muscularis in the

sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs (Figure 23.4). The peritoneal cavity is the space bounded by the visceral and parietal peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

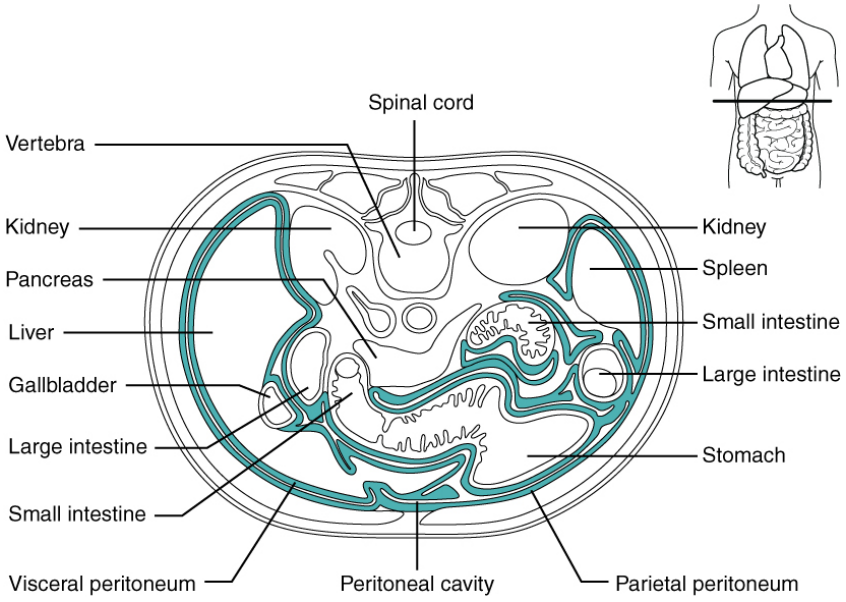


FIGURE 23.4 The Peritoneum A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

Disorders of the...

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in Table 23.2. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

Functions of the Digestive Organs

Organ	Major functions	Other functions
Mouth	• Ingests food • Chews and mixes food • Begins chemical breakdown of carbohydrates • Moves food into the pharynx • Begins breakdown of lipids via lingual lipase	• Moistens and dissolves food, allowing you to taste it • Cleans and lubricates the teeth and oral cavity • Has some antimicrobial activity
Pharynx	• Propels food from the oral cavity to the esophagus	• Lubricates food and passageways
Esophagus	• Propels food to the stomach	• Lubricates food and passageways
Stomach	• Mixes and churns food with gastric juices to form chyme • Begins chemical breakdown of proteins • Releases food into the duodenum as chyme • Absorbs some fat-soluble substances (for example, alcohol, aspirin) • Possesses antimicrobial functions	• Stimulates protein-digesting enzymes • Secretes intrinsic factor required for vitamin B_{12} absorption in small intestine
Small intestine	• Mixes chyme with digestive juices • Propels food at a rate slow enough for digestion and absorption • Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water • Performs physical digestion via segmentation	• Provides optimal medium for enzymatic activity
Accessory organs	• Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption • Gallbladder: stores, concentrates, and releases bile • Pancreas: produces digestive enzymes and bicarbonate	• Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity
Large intestine	• Further breaks down food residues • Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria • Propels feces toward rectum • Eliminates feces	• Food residue is concentrated and temporarily stored prior to defecation • Mucus eases passage of feces through colon

TABLE 23.3

Aging and the...

Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal (Figure 23.6).

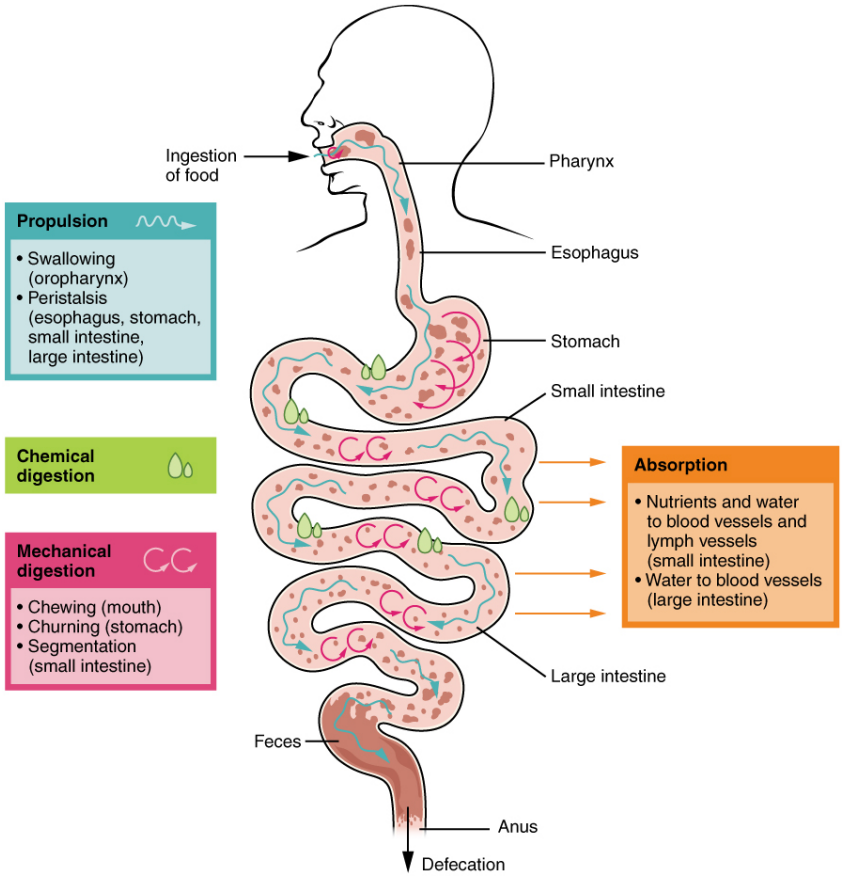


FIGURE 23.6 Digestive Processes The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for

they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The **labial frenulum** is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity's sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the **oral vestibule**. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the **fauces** (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the **soft palate**, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing (see Figure 23.7).

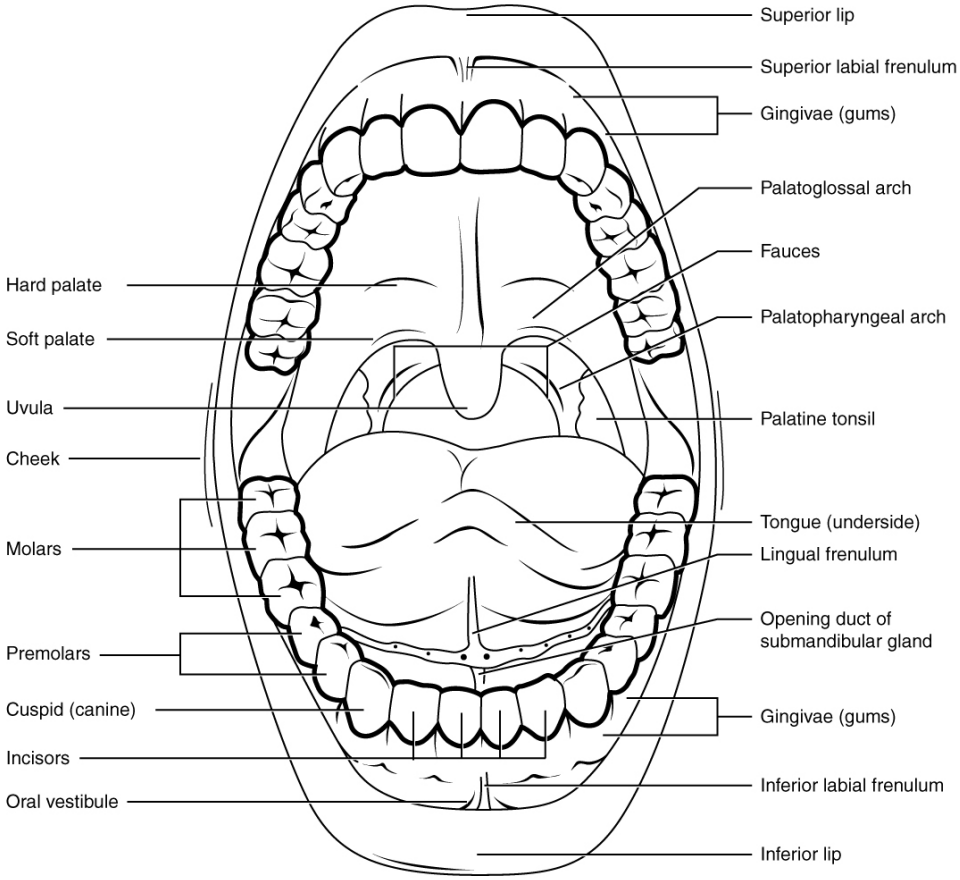


FIGURE 23.7 Mouth The mouth includes the lips, tongue, palate, gums, and teeth.

A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft

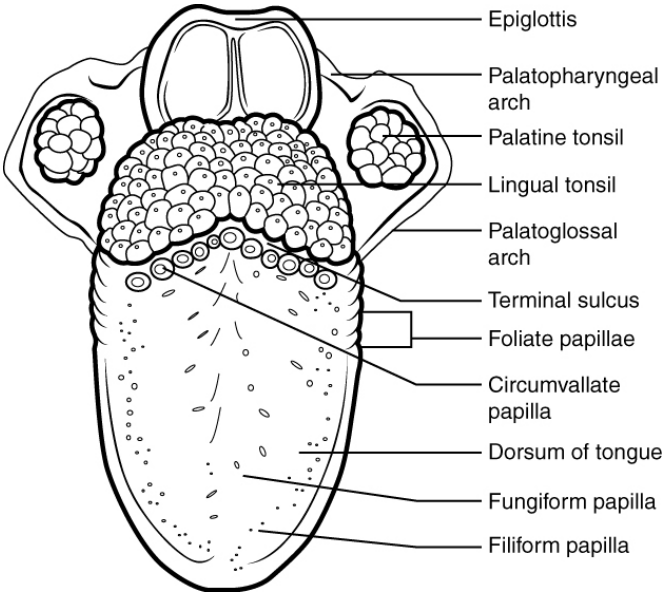


FIGURE 23.8 Tongue This superior view of the tongue shows the locations and types of lingual papillae.

The Salivary Glands

Many small **salivary glands** are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The **submandibular glands**, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The **sublingual glands**, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The **parotid glands** lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth (Figure 23.9).

Saliva

Saliva is essentially (98 to 99.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in saliva from the perspective of digestion is the enzyme **salivary amylase**, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage “a mother’s kiss can heal a wound.”

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.

The Teeth

The teeth, or **dentes** (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a **dentition**). Your 20 **deciduous teeth**, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 **permanent teeth**. Moving from the center of the mouth toward the side, these are as follows (Figure 23.10):

- The eight **incisors**, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four **cuspids** (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.
- Posterior to the cuspids are the eight **premolars** (or bicuspids), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 **molars**, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.

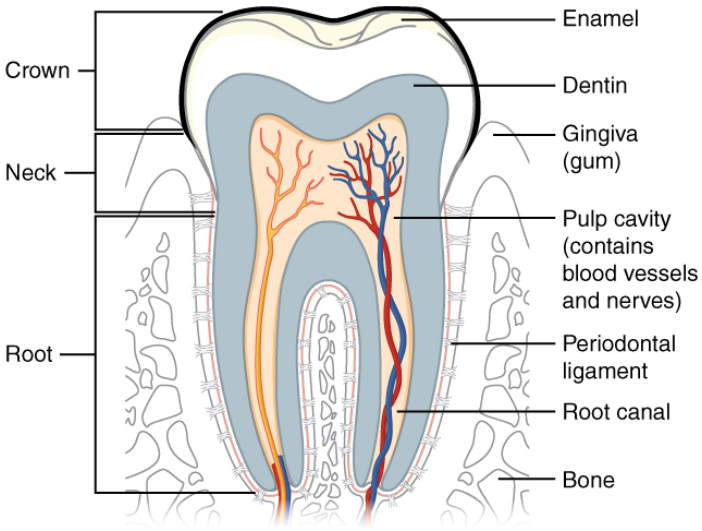


FIGURE 23.11 **The Structure of the Tooth** This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.

Digestive Functions of the Mouth

Structure	Action	Outcome
Lips and cheeks	Confine food between teeth	• Food is chewed evenly during mastication
Salivary glands	Secrete saliva	• Moisten and lubricate the lining of the mouth and pharynx • Moisten, soften, and dissolve food • Clean the mouth and teeth • Salivary amylase breaks down starch
Tongue's extrinsic muscles	Move tongue sideways, and in and out	• Manipulate food for chewing • Shape food into a bolus • Manipulate food for swallowing
Tongue's intrinsic muscles	Change tongue shape	• Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	• Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion
Lingual glands	Secrete lingual lipase	• Activated in the stomach • Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	• Break down solid food into smaller particles for deglutition

TABLE 23.4

length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in Figure 23.13, the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

Passage of Food through the Esophagus

The **upper esophageal sphincter**, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the **lower esophageal sphincter** (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

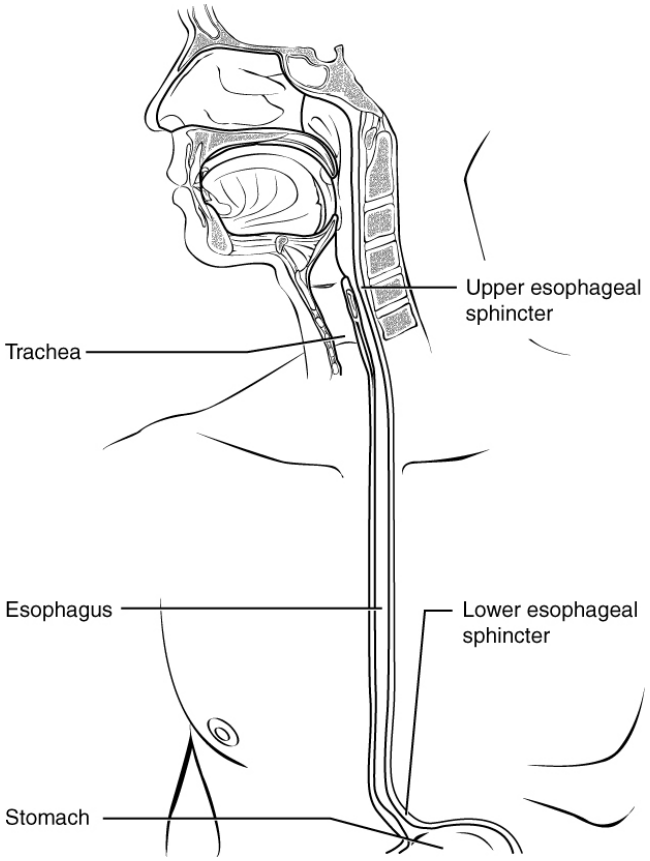


FIGURE 23.13 Esophagus The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa's lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in Table 23.5.

and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

INTERACTIVE LINK

Watch this animation (http://openstax.org/l/swallowing) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

23.4 The Stomach

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Label on a diagram the four main regions of the stomach, its curvatures, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the **stomach**: the cardia, fundus, body, and pylorus (Figure 23.15). The **cardia** (or

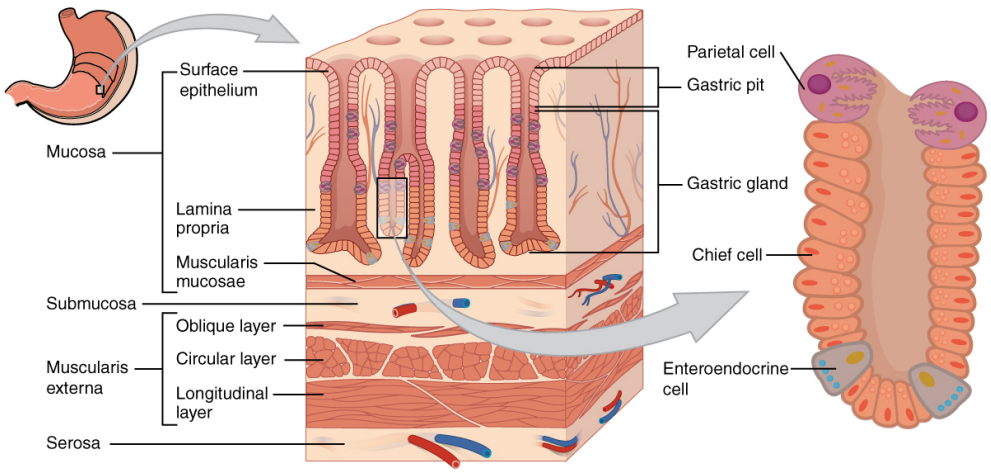


FIGURE 23.16 Histology of the Stomach The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric pits** dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located primarily in the middle region of the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B_{12} in the small intestine.

Chief cells—Located primarily in the basal regions of gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

Table 23.6 describes the digestive functions of important hormones secreted by the stomach.

INTERACTIVE LINK

Watch this animation (http://openstax.org/l/stomach1) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

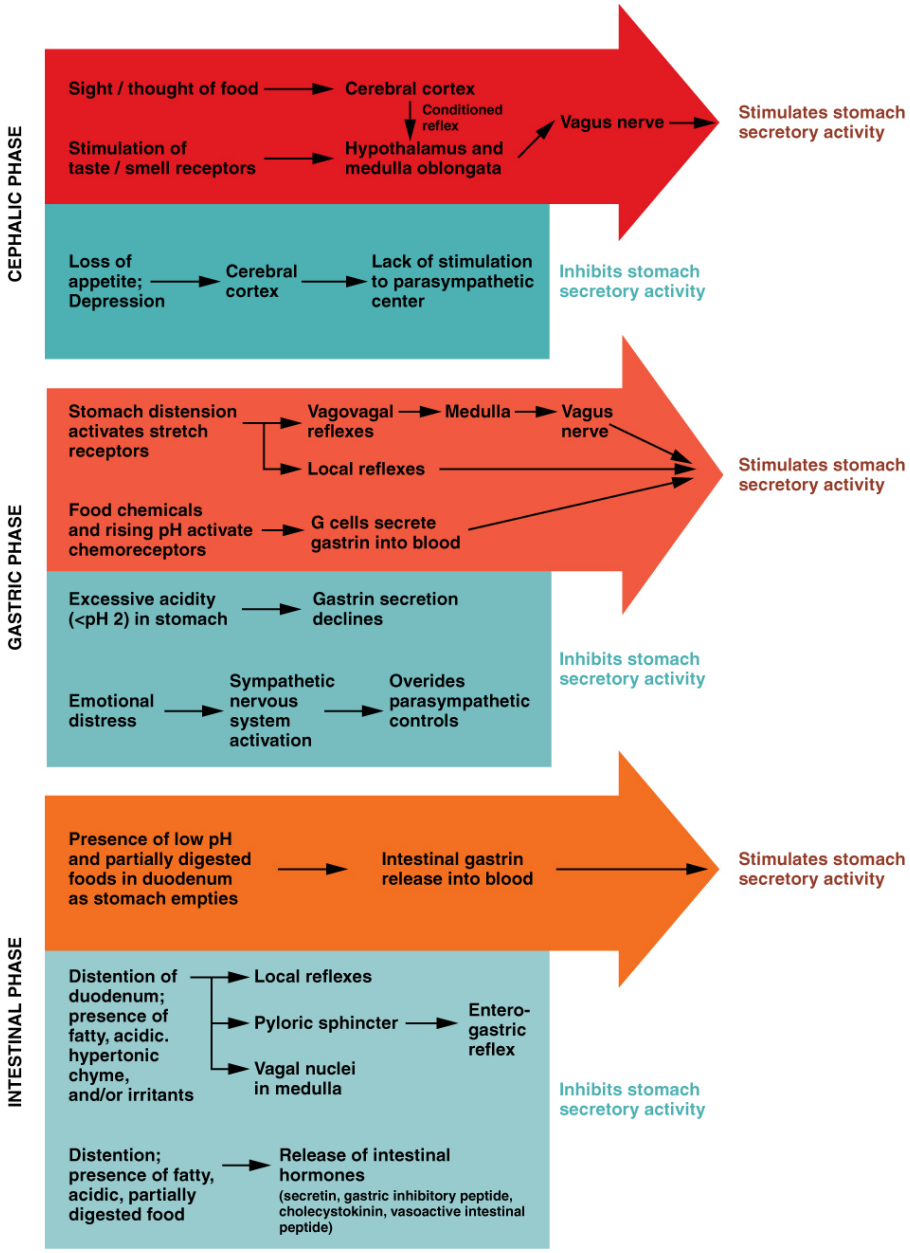


FIGURE 23.17 The Three Phases of Gastric Secretion Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential

process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12}, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B_{12} injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

23.5 The Small and Large Intestines

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning “internal,” and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the “guts,” they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m^2, more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

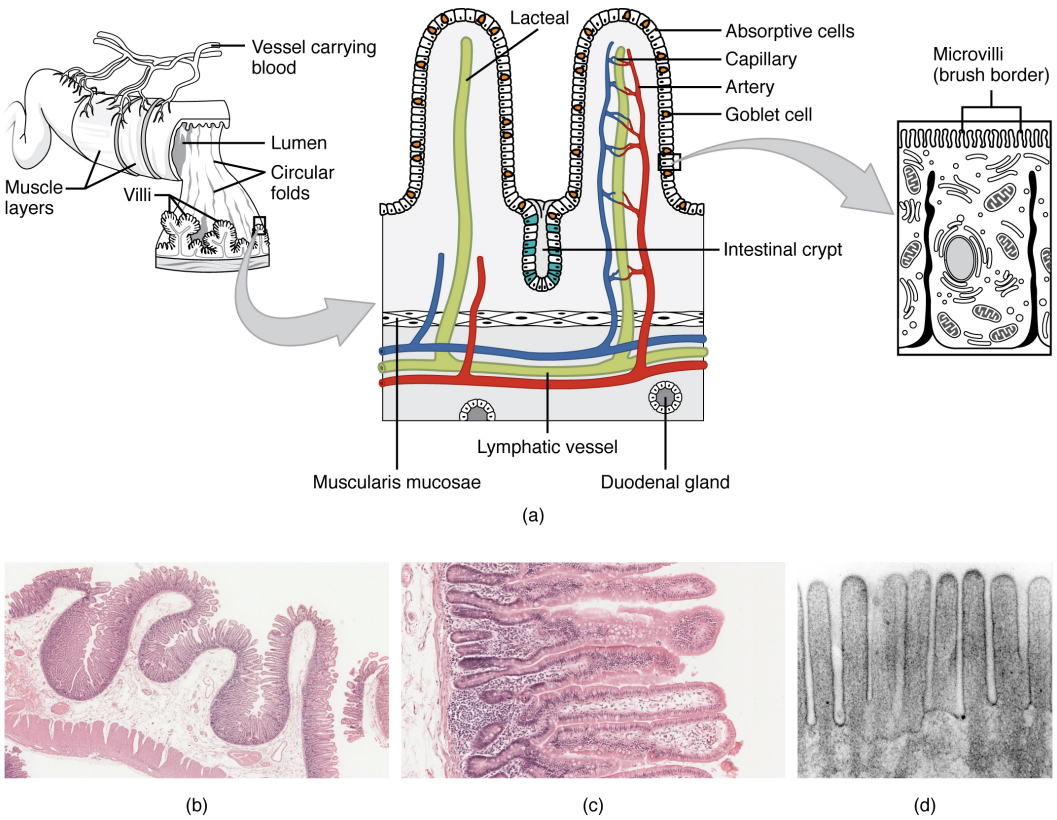


FIGURE 23.19 Histology of the Small Intestine (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Circular folds

Also called a plica circulare, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi** (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller (1 μm) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **intestinal gland** (crypt of Lieberkühn), which is formed by cells that line

Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute (Figure 23.20).

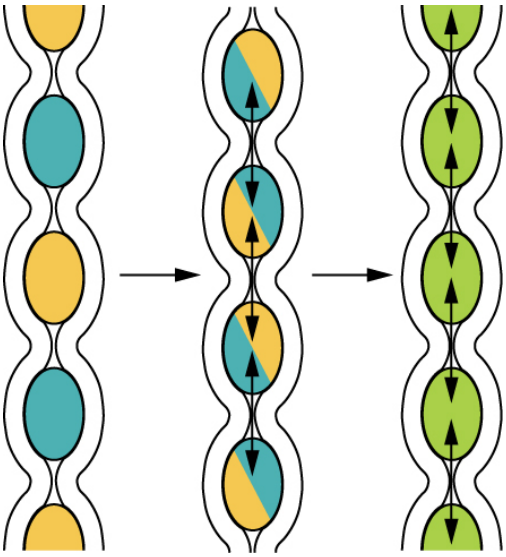


FIGURE 23.20 Segmentation Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal

Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the **right colic flexure** (hepatic flexure) and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the **left colic flexure** (splenic flexure). From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline (Figure 23.21). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

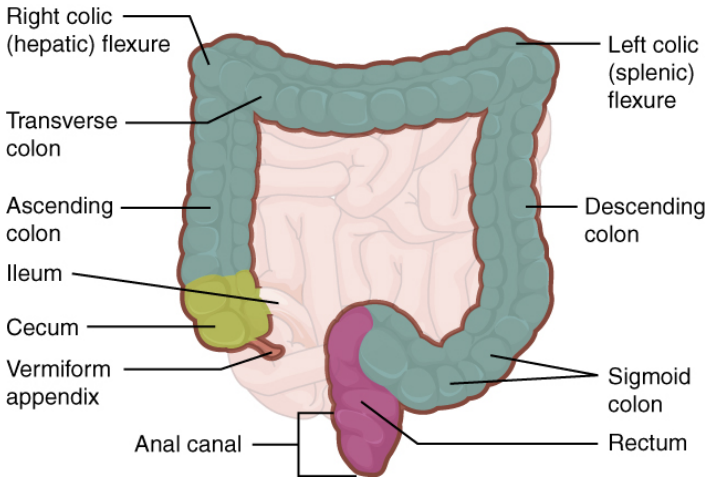


FIGURE 23.21 Large Intestine The large intestine includes the cecum, colon, and rectum.

HOMEOSTATIC IMBALANCES

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the **rectum** in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

Anal Canal

Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the

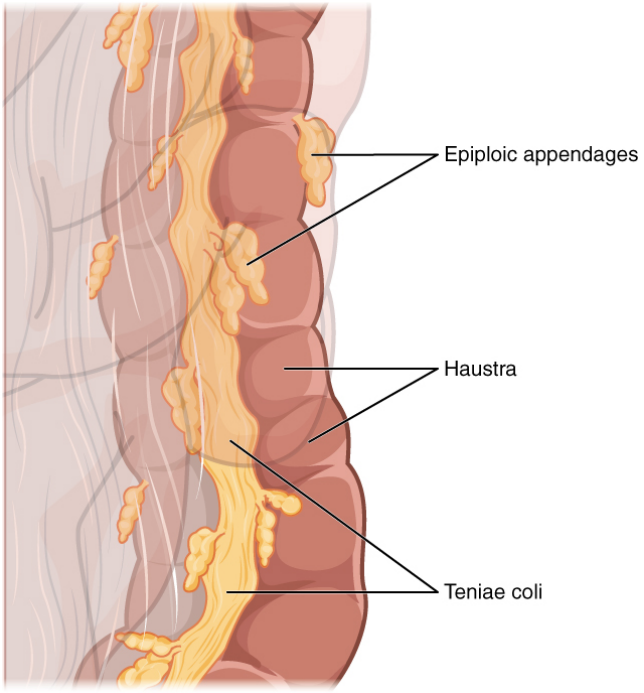


FIGURE 23.23 **Teniae Coli, Haustra, and Epiploic Appendages**

The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an **anal column**, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an **anal sinus**, secrete mucus that facilitates defecation. The **pectinate line** (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy.

INTERACTIVE LINK

By watching this animation (http://openstax.org/l/foodgroups) you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

23.6 Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- State the main digestive roles of the liver, pancreas, and gallbladder
- Identify three main features of liver histology that are critical to its function
- Discuss the composition and function of bile
- Identify the major types of enzymes and buffers present in pancreatic juice

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder (Figure 23.24). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

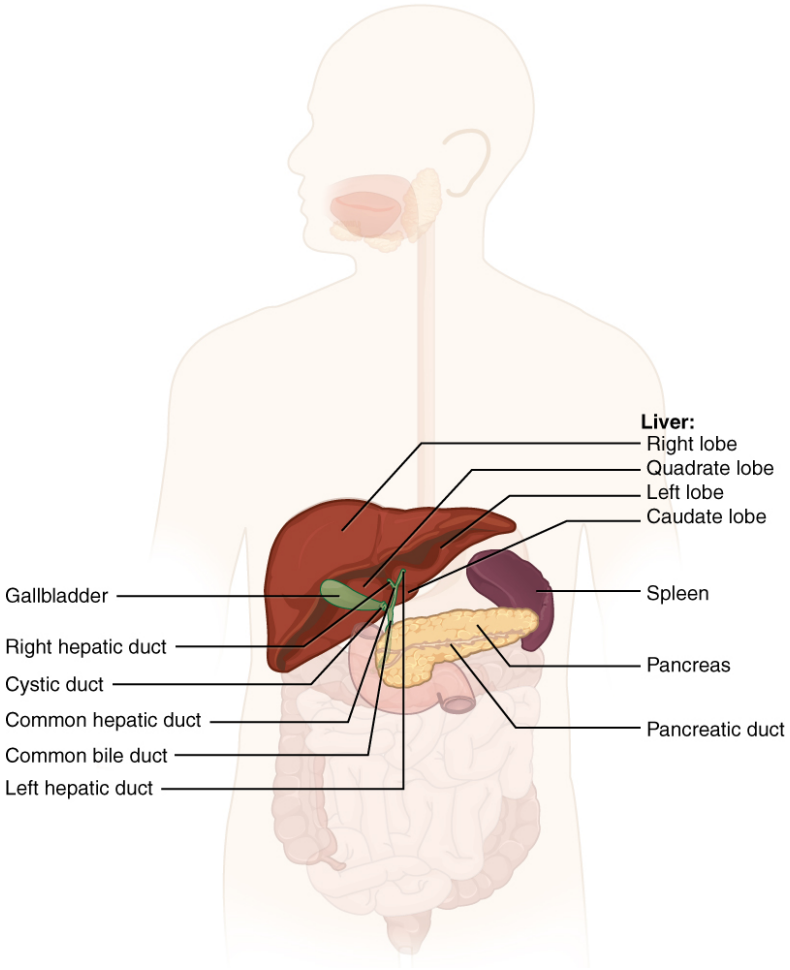


FIGURE 23.24 Accessory Organs The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most

Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A **hepatocyte** is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the portal vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

The Gallbladder

The **gallbladder** is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the **cystic duct** and into the bile duct (Figure 23.27). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

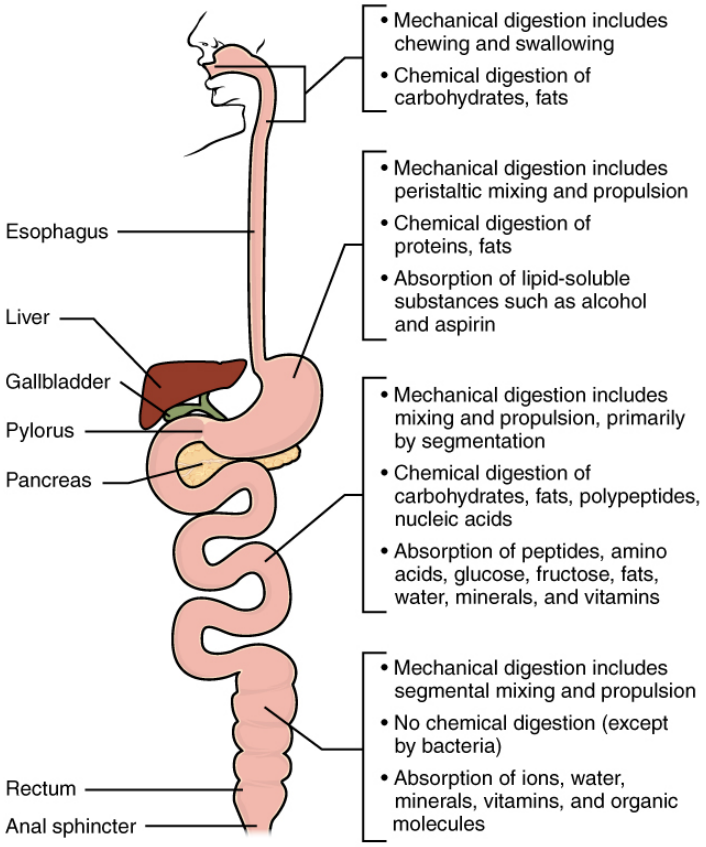


FIGURE 23.28 Digestion and Absorption Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in Table 23.8.

The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglycerides
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides

TABLE 23.8 *These enzymes have been activated by other substances.

Enzyme Category	Enzyme Name	Source	Substrate	Product
Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	α-Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

TABLE 23.8 *These enzymes have been activated by other substances.

Carbohydrate Digestion

The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the 'heavy lifting' for starch and carbohydrate digestion (Figure 23.29). After amylases break down starch into smaller fragments, the brush border enzyme **α-dextrinase** starts working on **α-dextrin**, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

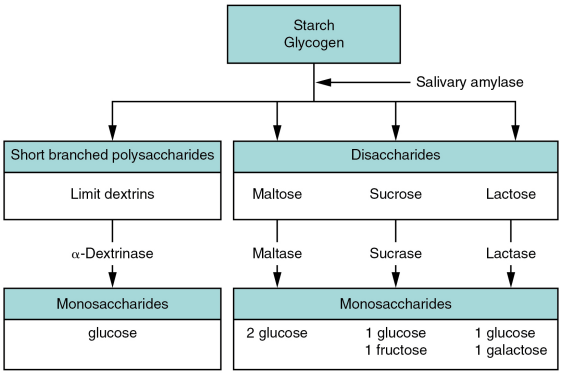


FIGURE 23.29 Carbohydrate Digestion Flow Chart Carbohydrates are broken down into their monomers in a series of steps.

Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

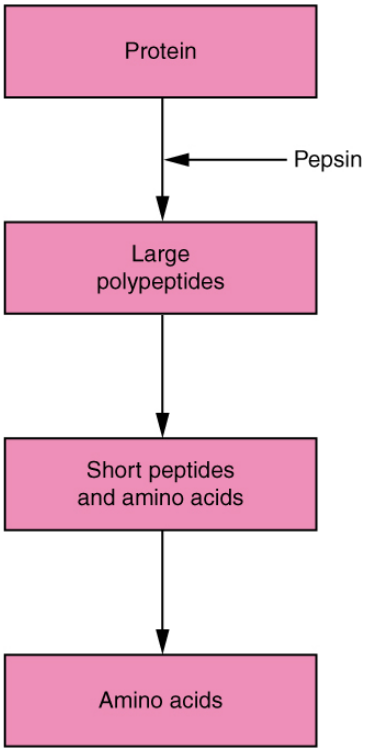


FIGURE 23.31 Digestion of Protein Flow Chart Proteins are successively broken down into their amino acid components.

Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

Nucleic Acid Digestion

The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (**nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized Table 23.9

Absorbable Food Substances

Source	Substance
Carbohydrates	Monosaccharides: glucose, galactose, and fructose
Proteins	Single amino acids, dipeptides, and tripeptides

TABLE 23.9

membrane act as "pumps," using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell's plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in Table 23.10.

Absorption in the Alimentary Canal

Food	Breakdown products	Absorption mechanism	Entry to bloodstream	Destination
Carbohydrates	Glucose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Fructose	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Monoacylglycerides	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Short-chain fatty acids	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein

TABLE 23.10

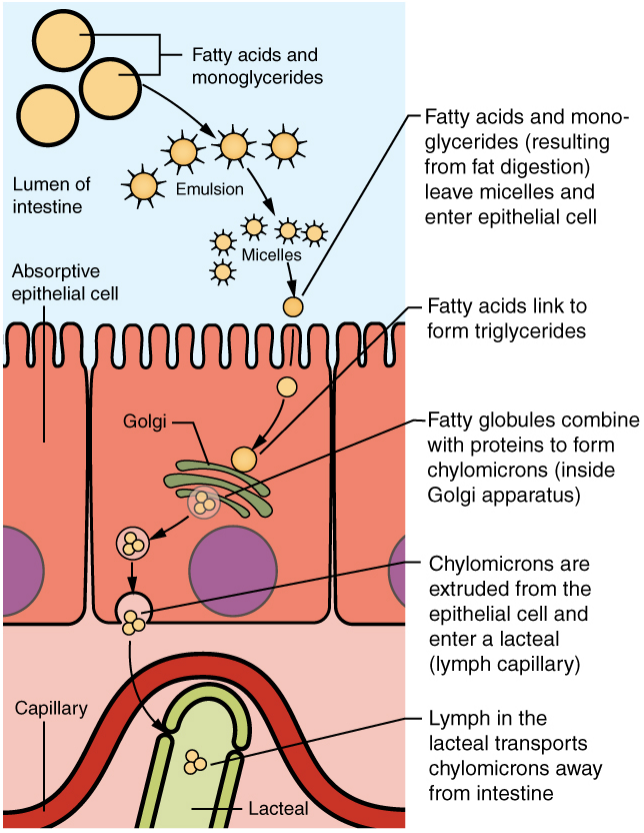


FIGURE 23.33 Lipid Absorption Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the bloodstream. Since females experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do males.

Calcium—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E,

Key Terms

absorption passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals
accessory digestive organ includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas
accessory duct (also, duct of Santorini) duct that runs from the pancreas into the duodenum
acinus cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas
alimentary canal continuous muscular digestive tube that extends from the mouth to the anus
aminopeptidase brush border enzyme that acts on proteins
anal canal final segment of the large intestine
anal column long fold of mucosa in the anal canal
anal sinus recess between anal columns
appendix (vermiform appendix) coiled tube attached to the cecum
ascending colon first region of the colon
bacterial flora bacteria in the large intestine
bile alkaline solution produced by the liver and important for the emulsification of lipids
bile canaliculus small duct between hepatocytes that collects bile
bilirubin main bile pigment, which is responsible for the brown color of feces
body mid-portion of the stomach
bolus mass of chewed food
brush border fuzzy appearance of the small intestinal mucosa created by microvilli
cardia (also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)
cecum pouch forming the beginning of the large intestine
cementum bone-like tissue covering the root of a tooth
central vein vein that receives blood from hepatic sinusoids
cephalic phase (also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach
chemical digestion enzymatic breakdown of food
chief cell gastric gland cell that secretes pepsinogen
chylomicron large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins
chyme soupy liquid created when food is mixed with digestive juices
circular fold (also, plica circulare) deep fold in the mucosa and submucosa of the small intestine
colon part of the large intestine between the cecum and the rectum
common bile duct structure formed by the union of the common hepatic duct and the gallbladder's cystic duct
common hepatic duct duct formed by the merger of the two hepatic ducts
crown portion of tooth visible superior to the gum line
cuspid (also, canine) pointed tooth used for tearing and shredding food
cystic duct duct through which bile drains and enters the gallbladder
deciduous tooth one of 20 "baby teeth"
defecation elimination of undigested substances from the body in the form of feces
deglutition three-stage process of swallowing
dens tooth
dentin bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth
dentition set of teeth
deoxyribonuclease pancreatic enzyme that digests DNA
descending colon part of the colon between the transverse colon and the sigmoid colon
dipeptidase brush border enzyme that acts on proteins
duodenal gland (also, Brunner's gland) mucous-secreting gland in the duodenal submucosa
duodenum first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum
enamel covering of the dentin of the crown of a tooth
enteroendocrine cell gastric gland cell that releases hormones
enterohepatic circulation recycling mechanism that conserves bile salts
enteropeptidase intestinal brush-border enzyme that activates trypsinogen to trypsin
epiploic appendage small sac of fat-filled visceral peritoneum attached to teniae coli
esophagus muscular tube that runs from the pharynx to the stomach
external anal sphincter voluntary skeletal muscle sphincter in the anal canal
fauces opening between the oral cavity and the oropharynx
feces semisolid waste product of digestion
flatus gas in the intestine
fundus dome-shaped region of the stomach above and to the left of the cardia
G cell gastrin-secreting enteroendocrine cell
gallbladder accessory digestive organ that stores and

monoacylglyceride core

microvillus small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex form of peristalsis in the small intestine

mixing wave unique type of peristalsis that occurs in the stomach

molar tooth used for crushing and grinding food

motilin hormone that initiates migrating motility complexes

motility movement of food through the GI tract

mucosa innermost lining of the alimentary canal

mucosal barrier protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell gastric gland cell that secretes a uniquely acidic mucus

muscularis muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus (plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

nucleosidase brush border enzyme that digests nucleotides

oral cavity (also, buccal cavity) mouth

oral vestibule part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

oropharynx part of the pharynx continuous with the oral cavity that functions in respiration and digestion

palatoglossal arch muscular fold that extends from the lateral side of the soft palate to the base of the tongue

palatopharyngeal arch muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

pancreas accessory digestive organ that secretes pancreatic juice

pancreatic amylase enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

pancreatic juice secretion of the pancreas containing digestive enzymes and bicarbonate

pancreatic lipase enzyme secreted by the pancreas that participates in lipid digestion

pancreatic nuclease enzyme secreted by the pancreas that participates in nucleic acid digestion

parietal cell gastric gland cell that secretes hydrochloric acid and intrinsic factor

parotid gland one of a pair of major salivary glands located inferior and anterior to the ears

pectinate line horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

pepsinogen inactive form of pepsin

peristalsis muscular contractions and relaxations that propel food through the GI tract

permanent tooth one of 32 adult teeth

pharynx throat

phosphatase brush border enzyme that digests nucleotides

porta hepatis "gateway to the liver" where the hepatic artery and hepatic portal vein enter the liver

portal triad bile duct, hepatic artery branch, and hepatic portal vein branch

premolar (also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

propulsion voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

pulp cavity deepest portion of a tooth, containing nerve endings and blood vessels

pyloric antrum wider, more superior part of the pylorus

pyloric canal narrow, more inferior part of the pylorus

pyloric sphincter sphincter that controls stomach emptying

pylorus lower, funnel-shaped part of the stomach that is continuous with the duodenum

rectal valve one of three transverse folds in the rectum where feces is separated from flatus

rectum part of the large intestine between the sigmoid colon and anal canal

reticuloendothelial cell (also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

retroperitoneal located posterior to the peritoneum

ribonuclease pancreatic enzyme that digests RNA

right colic flexure (also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

root portion of a tooth embedded in the alveolar processes beneath the gum line

ruga fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

saccharolytic fermentation anaerobic decomposition of carbohydrates

saliva aqueous solution of proteins and ions secreted into the mouth by the salivary glands

salivary amylase digestive enzyme in saliva that acts on starch

salivary gland an exocrine gland that secretes a digestive fluid called saliva

salivation secretion of saliva

segmentation alternating contractions and relaxations of non-adjacent segments of the

releases it gradually into the small intestine through the pyloric sphincter.

23.5 The Small and Large Intestines

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption. Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

23.6 Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

23.7 Chemical Digestion and Absorption: A Closer Look

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

Interactive Link Questions

1. By clicking on this link (http://openstax.org/l/fooddigestion), you can watch a short video of what happens to the food you eat as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?
2. Visit this site (http://openstax.org/l/fooddigestion2) for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.
3. Watch this animation (http://openstax.org/l/swallowing) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?
4. Watch this animation (http://openstax.org/l/stomach1) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

17. Which structure is located where the esophagus penetrates the diaphragm?
a. esophageal hiatus
b. cardiac orifice
c. upper esophageal sphincter
d. lower esophageal sphincter

18. Which phase of deglutition involves contraction of the longitudinal muscle layer of the muscularis?
a. voluntary phase
b. buccal phase
c. pharyngeal phase
d. esophageal phase

19. Which of these cells secrete hormones?
a. parietal cells
b. mucous neck cells
c. enteroendocrine cells
d. chief cells

20. Where does the majority of chemical digestion in the stomach occur?
a. fundus and body
b. cardia and fundus
c. body and pylorus
d. body

21. During gastric emptying, chyme is released into the duodenum through the _____.
a. esophageal hiatus
b. pyloric antrum
c. pyloric canal
d. pyloric sphincter

22. Parietal cells secrete _____.
a. gastrin
b. hydrochloric acid
c. pepsin
d. pepsinogen

23. In which part of the alimentary canal does most digestion occur?
a. stomach
b. proximal small intestine
c. distal small intestine
d. ascending colon

24. Which of these is most associated with villi?
a. haustra
b. lacteals
c. bacterial flora
d. intestinal glands

25. What is the role of the small intestine's MALT?
a. secreting mucus
b. buffering acidic chyme
c. activating pepsin
d. preventing bacteria from entering the bloodstream

26. Which part of the large intestine attaches to the appendix?
a. cecum
b. ascending colon
c. transverse colon
d. descending colon

27. Which of these statements about bile is true?
a. About 500 mL is secreted daily.
b. Its main function is the denaturation of proteins.
c. It is synthesized in the gallbladder.
d. Bile salts are recycled.

28. Pancreatic juice _____.
a. deactivates bile.
b. is secreted by pancreatic islet cells.
c. buffers chyme.
d. is released into the cystic duct.

29. Where does the chemical digestion of starch begin?
a. mouth
b. esophagus
c. stomach
d. small intestine

30. Which of these is involved in the chemical digestion of protein?
a. pancreatic amylase
b. trypsin
c. sucrase
d. pancreatic nuclease

31. Where are most fat-digesting enzymes produced?
a. small intestine
b. gallbladder
c. liver
d. pancreas

32. Which of these nutrients is absorbed mainly in the duodenum?
a. glucose
b. iron
c. sodium
d. water

proteins and enzymes derived from their genetic background. Thus, your genes play a big role in your metabolism. Nonetheless, each person's body engages in the same overall metabolic processes.

24.1 Overview of Metabolic Reactions

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the process by which polymers are broken down into monomers
- Describe the process by which monomers are combined into polymers
- Discuss the role of ATP in metabolism
- Explain oxidation-reduction reactions
- Describe the hormones that regulate anabolic and catabolic reactions

Metabolic processes are constantly taking place in the body. **Metabolism** is the sum of all of the chemical reactions that are involved in catabolism and anabolism. The reactions governing the breakdown of food to obtain energy are called catabolic reactions. Conversely, anabolic reactions use the energy produced by catabolic reactions to synthesize larger molecules from smaller ones, such as when the body forms proteins by stringing together amino acids. Both sets of reactions are critical to maintaining life.

Because catabolic reactions produce energy and anabolic reactions use energy, ideally, energy usage would balance the energy produced. If the net energy change is positive (catabolic reactions release more energy than the anabolic reactions use), then the body stores the excess energy by building fat molecules for long-term storage. On the other hand, if the net energy change is negative (catabolic reactions release less energy than anabolic reactions use), the body uses stored energy to compensate for the deficiency of energy released by catabolism.

Catabolic Reactions

Catabolic reactions break down large organic molecules into smaller molecules, releasing the energy contained in the chemical bonds. These energy releases (conversions) are not 100 percent efficient. The amount of energy released is less than the total amount contained in the molecule. Approximately 40 percent of energy yielded from catabolic reactions is directly transferred to the high-energy molecule adenosine triphosphate (ATP). ATP, the energy currency of cells, can be used immediately to power molecular machines that support cell, tissue, and organ function. This includes building new tissue and repairing damaged tissue. ATP can also be stored to fulfill future energy demands. The remaining 60 percent of the energy released from catabolic reactions is given off as heat, which tissues and body fluids absorb.

Structurally, ATP molecules consist of an adenine, a ribose, and three phosphate groups (Figure 24.2). The chemical bond between the second and third phosphate groups, termed a high-energy bond, represents the greatest source of energy in a cell. It is the first bond that catabolic enzymes break when cells require energy to do work. The products of this reaction are a molecule of adenosine diphosphate (ADP) and a lone phosphate group (P_i). ATP, ADP, and P_i are constantly being cycled through reactions that build ATP and store energy, and reactions that break down ATP and release energy.

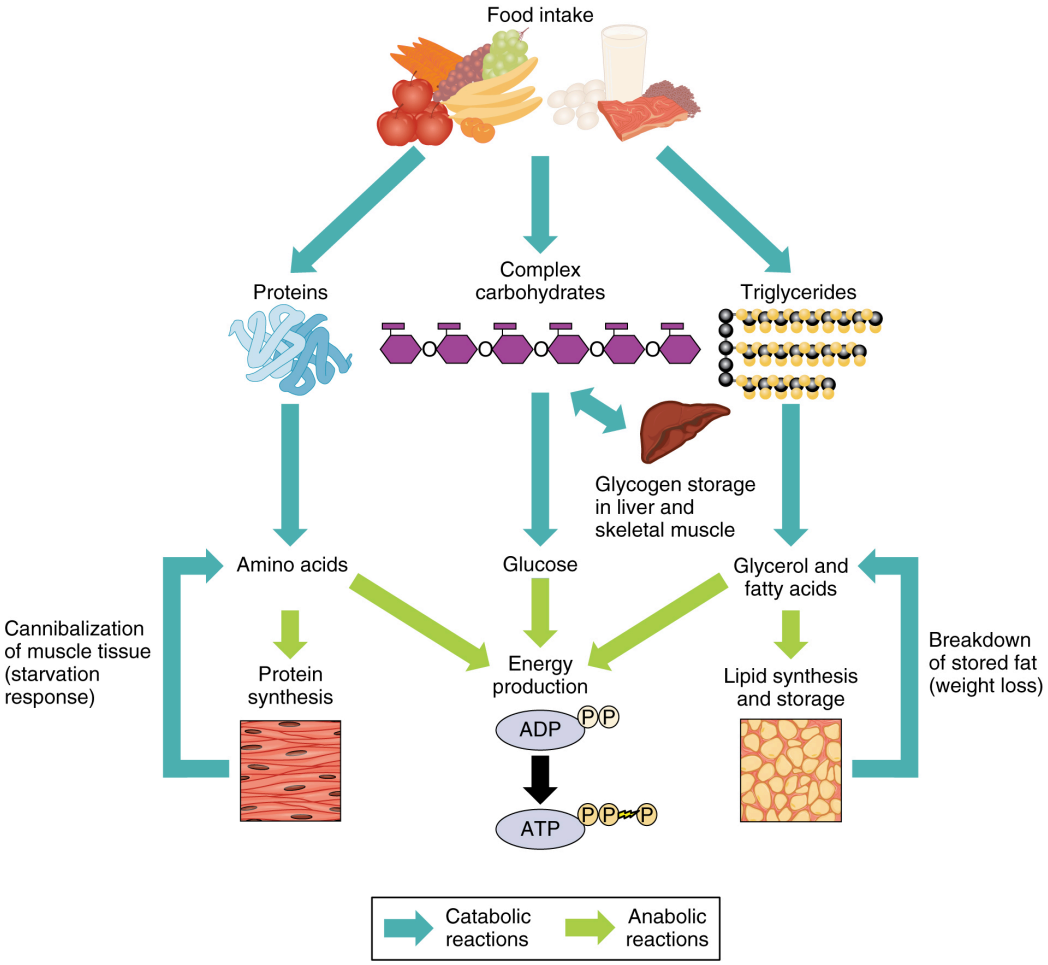


FIGURE 24.3 Sources of ATP During catabolic reactions, proteins are broken down into amino acids, lipids are broken down into fatty acids, and polysaccharides are broken down into monosaccharides. These building blocks are then used for the synthesis of molecules in anabolic reactions.

Of the four major macromolecular groups (carbohydrates, lipids, proteins, and nucleic acids) that are processed by digestion, carbohydrates are considered the most common source of energy to fuel the body. They take the form of either complex carbohydrates, polysaccharides like starch and glycogen, or simple sugars (monosaccharides) like glucose and fructose. Sugar catabolism breaks polysaccharides down into their individual monosaccharides. Among the monosaccharides, glucose is the most common fuel for ATP production in cells, and as such, there are a number of endocrine control mechanisms to regulate glucose concentration in the bloodstream. Excess glucose is either stored as an energy reserve in the liver and skeletal muscles as the complex polymer glycogen, or it is converted into fat (triglyceride) in adipose cells (adipocytes).

Among the lipids (fats), triglycerides are most often used for energy via a metabolic process called β-oxidation. About one-half of excess fat is stored in adipocytes that accumulate in the subcutaneous tissue under the skin, whereas the rest is stored in adipocytes in other tissues and organs.

Proteins, which are polymers, can be broken down into their monomers, individual amino acids. Amino acids can be used as building blocks of new proteins or broken down further for the production of ATP. When one is chronically starving, this use of amino acids for energy production can lead to a wasting away of the body, as more and more proteins are broken down.

Nucleic acids are present in most of the foods you eat. During digestion, nucleic acids including DNA and various RNAs are broken down into their constituent nucleotides. These nucleotides are readily absorbed and transported throughout the body to be used by individual cells during nucleic acid metabolism.

Hormone	Function
Testosterone	Produced by the testes in males and the ovaries in females; stimulates an increase in muscle mass and strength as well as the growth and strengthening of bone
Estrogen	Produced primarily by the ovaries, it is also produced by the liver and adrenal glands; its anabolic functions include increasing metabolism and fat deposition

TABLE 24.2

Disorders of the...

Metabolic Processes: Cushing Syndrome and Addison's Disease

As might be expected for a fundamental physiological process like metabolism, errors or malfunctions in metabolic processing lead to a pathophysiology or—if uncorrected—a disease state. Metabolic diseases are most commonly the result of malfunctioning proteins or enzymes that are critical to one or more metabolic pathways. Protein or enzyme malfunction can be the consequence of a genetic alteration or mutation. However, normally functioning proteins and enzymes can also have deleterious effects if their availability is not appropriately matched with metabolic need. For example, excessive production of the hormone cortisol (see Table 24.1) gives rise to Cushing syndrome. Clinically, Cushing syndrome is characterized by rapid weight gain, especially in the trunk and face region, depression, and anxiety. It is worth mentioning that tumors of the pituitary that produce adrenocorticotropic hormone (ACTH), which subsequently stimulates the adrenal cortex to release excessive cortisol, produce similar effects. This indirect mechanism of cortisol overproduction is referred to as Cushing disease.

Patients with Cushing syndrome can exhibit high blood glucose levels and are at an increased risk of becoming obese. They also show slow growth, accumulation of fat between the shoulders, weak muscles, bone pain (because cortisol causes proteins to be broken down to make glucose via gluconeogenesis), and fatigue. Other symptoms include excessive sweating (hyperhidrosis), capillary dilation, and thinning of the skin, which can lead to easy bruising. The treatments for Cushing syndrome are all focused on reducing excessive cortisol levels. Depending on the cause of the excess, treatment may be as simple as discontinuing the use of cortisol ointments. In cases of tumors, surgery is often used to remove the offending tumor. Where surgery is inappropriate, radiation therapy can be used to reduce the size of a tumor or ablate portions of the adrenal cortex. Finally, medications are available that can help to regulate the amounts of cortisol.

Insufficient cortisol production is equally problematic. Adrenal insufficiency, or Addison's disease, is characterized by the reduced production of cortisol from the adrenal gland. It can result from malfunction of the adrenal glands—they do not produce enough cortisol—or it can be a consequence of decreased ACTH availability from the pituitary. Patients with Addison's disease may have low blood pressure, paleness, extreme weakness, fatigue, slow or sluggish movements, lightheadedness, and salt cravings due to the loss of sodium and high blood potassium levels (hyperkalemia). Victims also may suffer from loss of appetite, chronic diarrhea, vomiting, mouth lesions, and patchy skin color. Diagnosis typically involves blood tests and imaging tests of the adrenal and pituitary glands. Treatment involves cortisol replacement therapy, which usually must be continued for life.

Oxidation-Reduction Reactions

The chemical reactions underlying metabolism involve the transfer of electrons from one compound to another by processes catalyzed by enzymes. The electrons in these reactions commonly come from hydrogen atoms, which consist of an electron and a proton. A molecule gives up a hydrogen atom, in the form of a hydrogen ion (H^+) and an electron, breaking the molecule into smaller parts. The loss of an electron, or **oxidation**, releases a small amount of energy; both the electron and the energy are then passed to another molecule in the process of **reduction**, or the gaining of an electron. These two reactions always happen together in an **oxidation-reduction reaction** (also called a redox reaction)—when an electron is passed between molecules, the donor is oxidized and the recipient is reduced. Oxidation-reduction reactions often happen in a series, so that a molecule that is reduced is subsequently

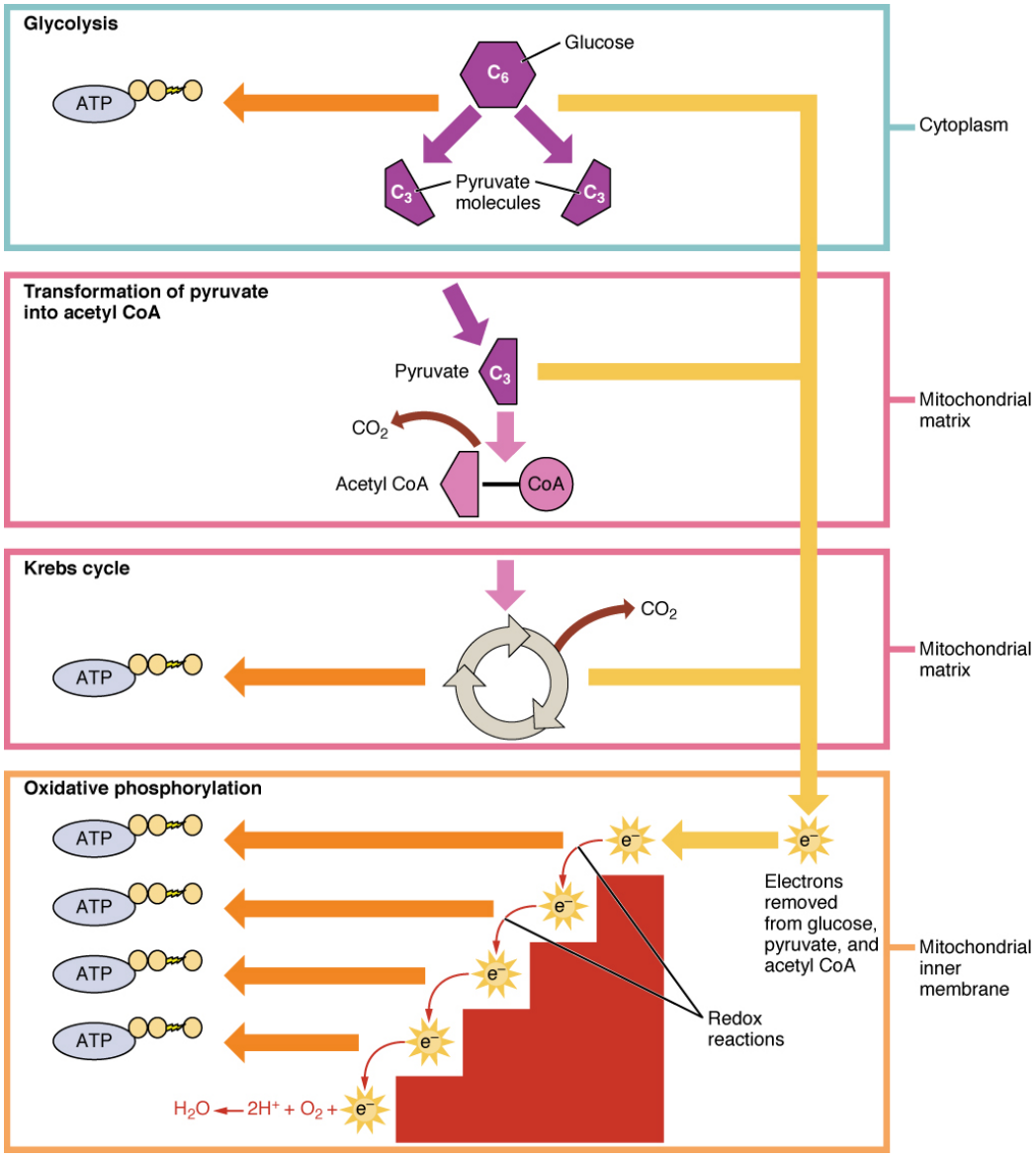


FIGURE 24.4 Cellular Respiration Cellular respiration oxidizes glucose molecules through glycolysis, the Krebs cycle, and oxidative phosphorylation to produce ATP.

Glycolysis

Glucose is the body's most readily available source of energy. After digestive processes break polysaccharides down into monosaccharides, including glucose, the monosaccharides are transported across the wall of the small intestine and into the circulatory system, which transports them to the liver. In the liver, hepatocytes either pass the glucose on through the circulatory system or store excess glucose as glycogen. Cells in the body take up the circulating glucose in response to insulin and, through a series of reactions called **glycolysis**, transfer some of the energy in glucose to ADP to form ATP (Figure 24.5). The last step in glycolysis produces the product **pyruvate**.

Glycolysis begins with the phosphorylation of glucose by hexokinase to form glucose-6-phosphate. This step uses one ATP, which is the donor of the phosphate group. Under the action of phosphofructokinase, glucose-6-phosphate is converted into fructose-6-phosphate. At this point, a second ATP donates its phosphate group, forming fructose-1,6-bisphosphate. This six-carbon sugar is split to form two phosphorylated three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are both converted into glyceraldehyde-3-phosphate. The glyceraldehyde-3-phosphate is further phosphorylated with groups donated by dihydrogen phosphate present in the cell to form the three-carbon molecule 1,3-bisphosphoglycerate. The energy of this reaction comes from the oxidation of (removal of electrons from) glyceraldehyde-3-phosphate. In a series of

INTERACTIVE LINK

Watch this video (http://openstax.org/l/glycolysis1) to learn about glycolysis.

Glycolysis can be divided into two phases: energy consuming (also called chemical priming) and energy yielding. The first phase is the **energy-consuming phase**, so it requires two ATP molecules to start the reaction for each molecule of glucose. However, the end of the reaction produces four ATPs, resulting in a net gain of two ATP energy molecules.

Glycolysis can be expressed as the following equation:

$$\text{Glucose} + 2\text{ATP} + 2\text{NAD}^+ + 4\text{ADP} + 2\text{P}_i \rightarrow 2\ \text{Pyruvate} + 4\text{ATP} + 2\text{NADH} + 2\text{H}^+$$

This equation states that glucose, in combination with ATP (the energy source), NAD^+ (a coenzyme that serves as an electron acceptor), and inorganic phosphate, breaks down into two pyruvate molecules, generating four ATP molecules—for a net yield of two ATP—and two energy-containing NADH coenzymes. The NADH that is produced in this process will be used later to produce ATP in the mitochondria. Importantly, by the end of this process, one glucose molecule generates two pyruvate molecules, two high-energy ATP molecules, and two electron-carrying NADH molecules.

The following discussions of glycolysis include the enzymes responsible for the reactions. When glucose enters a cell, the enzyme hexokinase (or glucokinase, in the liver) rapidly adds a phosphate to convert it into **glucose-6-phosphate**. A kinase is a type of enzyme that adds a phosphate molecule to a substrate (in this case, glucose, but it can be true of other molecules also). This conversion step requires one ATP and essentially traps the glucose in the cell, preventing it from passing back through the plasma membrane, thus allowing glycolysis to proceed. It also functions to maintain a concentration gradient with higher glucose levels in the blood than in the tissues. By establishing this concentration gradient, the glucose in the blood will be able to flow from an area of high concentration (the blood) into an area of low concentration (the tissues) to be either used or stored. **Hexokinase** is found in nearly every tissue in the body. **Glucokinase**, on the other hand, is expressed in tissues that are active when blood glucose levels are high, such as the liver. Hexokinase has a higher affinity for glucose than glucokinase and therefore is able to convert glucose at a faster rate than glucokinase. This is important when levels of glucose are very low in the body, as it allows glucose to travel preferentially to those tissues that require it more.

In the next step of the first phase of glycolysis, the enzyme glucose-6-phosphate isomerase converts glucose-6-phosphate into fructose-6-phosphate. Like glucose, fructose is also a six carbon-containing sugar. The enzyme phosphofructokinase-1 then adds one more phosphate to convert fructose-6-phosphate into fructose-1-6-bisphosphate, another six-carbon sugar, using another ATP molecule. Aldolase then breaks down this fructose-1-6-bisphosphate into two three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The triosephosphate isomerase enzyme then converts dihydroxyacetone phosphate into a second glyceraldehyde-3-phosphate molecule. Therefore, by the end of this chemical-priming or energy-consuming phase, one glucose molecule is broken down into two glyceraldehyde-3-phosphate molecules.

The second phase of glycolysis, the **energy-yielding phase**, creates the energy that is the product of glycolysis. Glyceraldehyde-3-phosphate dehydrogenase converts each three-carbon glyceraldehyde-3-phosphate produced during the energy-consuming phase into 1,3-bisphosphoglycerate. This reaction releases an electron that is then picked up by NAD^+ to create an NADH molecule. NADH is a high-energy molecule, like ATP, but unlike ATP, it is not used as energy currency by the cell. Because there are two glyceraldehyde-3-phosphate molecules, two NADH molecules are synthesized during this step. Each 1,3-bisphosphoglycerate is subsequently dephosphorylated (i.e., a phosphate is removed) by phosphoglycerate kinase into 3-phosphoglycerate. Each phosphate released in this reaction can convert one molecule of ADP into one high-energy ATP molecule, resulting in a gain of two ATP molecules.

The enzyme phosphoglycerate mutase then converts the 3-phosphoglycerate molecules into 2-phosphoglycerate. The enolase enzyme then acts upon the 2-phosphoglycerate molecules to convert them into phosphoenolpyruvate molecules. The last step of glycolysis involves the dephosphorylation of the two phosphoenolpyruvate molecules by pyruvate kinase to create two pyruvate molecules and two ATP molecules.

In summary, one glucose molecule breaks down into two pyruvate molecules, and creates two net ATP molecules

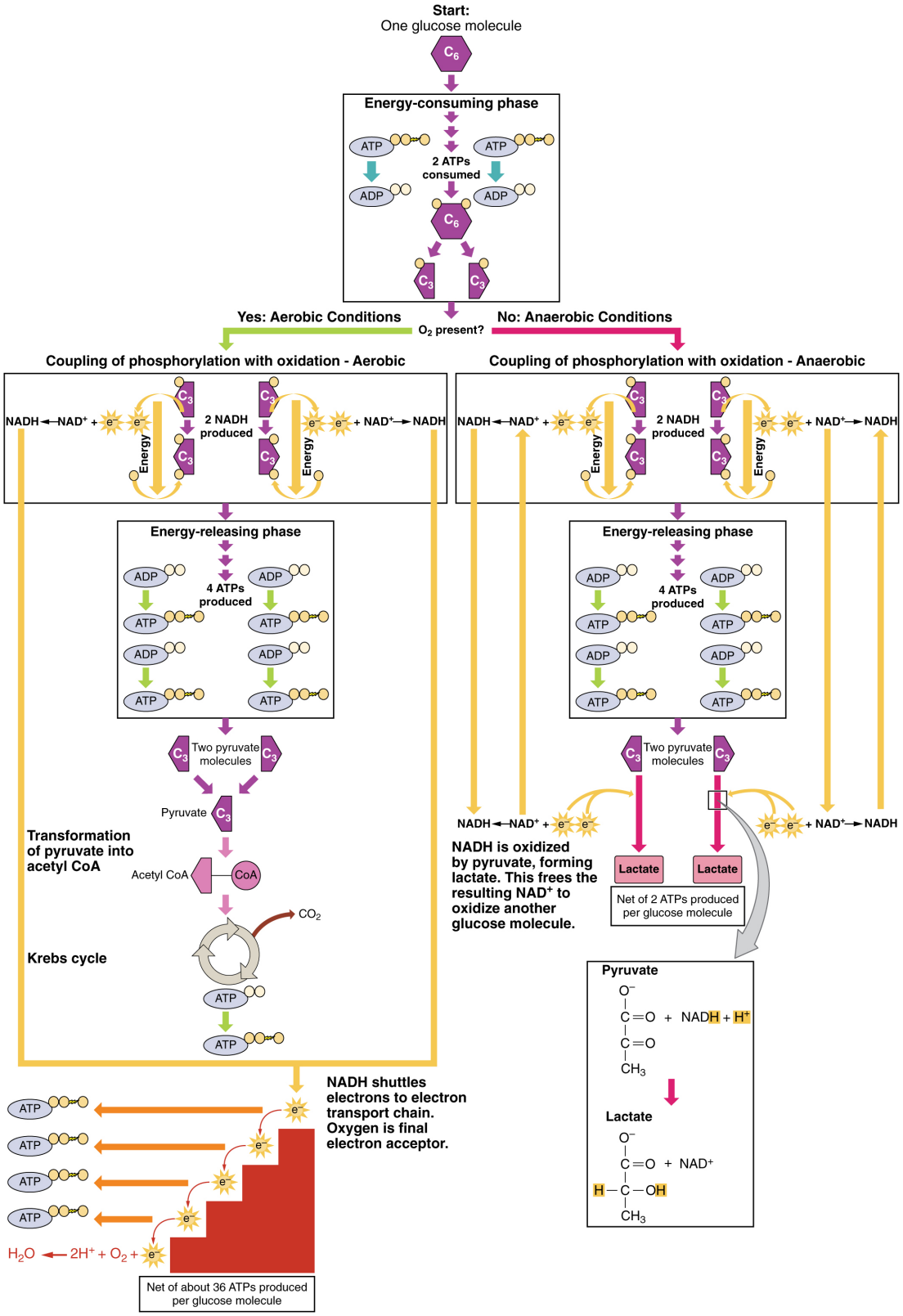


FIGURE 24.6 Aerobic versus Anaerobic Respiration The process of anaerobic respiration converts glucose into two lactate molecules in the absence of oxygen or within erythrocytes that lack mitochondria. During aerobic respiration, glucose is oxidized into two pyruvate molecules.

Krebs Cycle/Citric Acid Cycle/Tricarboxylic Acid Cycle

The pyruvate molecules generated during glycolysis are transported across the mitochondrial membrane into the

two-carbon acetyl CoA molecule, releasing carbon dioxide and transferring two electrons that combine with NAD^+ to form NADH. Acetyl CoA enters the Krebs cycle by combining with a four-carbon molecule, oxaloacetate, to form the six-carbon molecule citrate, or citric acid, at the same time releasing the coenzyme A molecule.

The six-carbon citrate molecule is systematically converted to a five-carbon molecule and then a four-carbon molecule, ending with oxaloacetate, the beginning of the cycle. Along the way, each citrate molecule will produce one ATP, one $FADH_2$, and three NADH. The $FADH_2$ and NADH will enter the oxidative phosphorylation system located in the inner mitochondrial membrane. In addition, the Krebs cycle supplies the starting materials to process and break down proteins and fats.

To start the Krebs cycle, citrate synthase combines acetyl CoA and oxaloacetate to form a six-carbon citrate molecule; CoA is subsequently released and can combine with another pyruvate molecule to begin the cycle again. The aconitase enzyme converts citrate into isocitrate. In two successive steps of oxidative decarboxylation, two molecules of CO_2 and two NADH molecules are produced when isocitrate dehydrogenase converts isocitrate into the five-carbon α-ketoglutarate, which is then catalyzed and converted into the four-carbon succinyl CoA by α-ketoglutarate dehydrogenase. The enzyme succinyl CoA dehydrogenase then converts succinyl CoA into succinate and forms the high-energy molecule GTP, which transfers its energy to ADP to produce ATP. Succinate dehydrogenase then converts succinate into fumarate, forming a molecule of $FADH_2$. Fumarase then converts fumarate into malate, which malate dehydrogenase then converts back into oxaloacetate while reducing NAD^+ to NADH. Oxaloacetate is then ready to combine with the next acetyl CoA to start the Krebs cycle again (see Figure 24.7). For each turn of the cycle, three NADH, one ATP (through GTP), and one $FADH_2$ are created. Each carbon of pyruvate is converted into CO_2, which is released as a byproduct of oxidative (aerobic) respiration.

Oxidative Phosphorylation and the Electron Transport Chain

The **electron transport chain (ETC)** uses the NADH and $FADH_2$ produced by the Krebs cycle to generate ATP. Electrons from NADH and $FADH_2$ are transferred through protein complexes embedded in the inner mitochondrial membrane by a series of enzymatic reactions. The electron transport chain consists of a series of four enzyme complexes (Complex I – Complex IV) and two coenzymes (ubiquinone and Cytochrome c), which act as electron carriers and proton pumps used to transfer H^+ ions into the space between the inner and outer mitochondrial membranes (Figure 24.8). The ETC couples the transfer of electrons between a donor (like NADH) and an electron acceptor (like O_2) with the transfer of protons (H^+ ions) across the inner mitochondrial membrane, enabling the process of **oxidative phosphorylation**. In the presence of oxygen, energy is passed, stepwise, through the electron carriers to collect gradually the energy needed to attach a phosphate to ADP and produce ATP. The role of molecular oxygen, O_2, is as the terminal electron acceptor for the ETC. This means that once the electrons have passed through the entire ETC, they must be passed to another, separate molecule. These electrons, O_2, and H^+ ions from the matrix combine to form new water molecules. This is the basis for your need to breathe in oxygen. Without oxygen, electron flow through the ETC ceases.

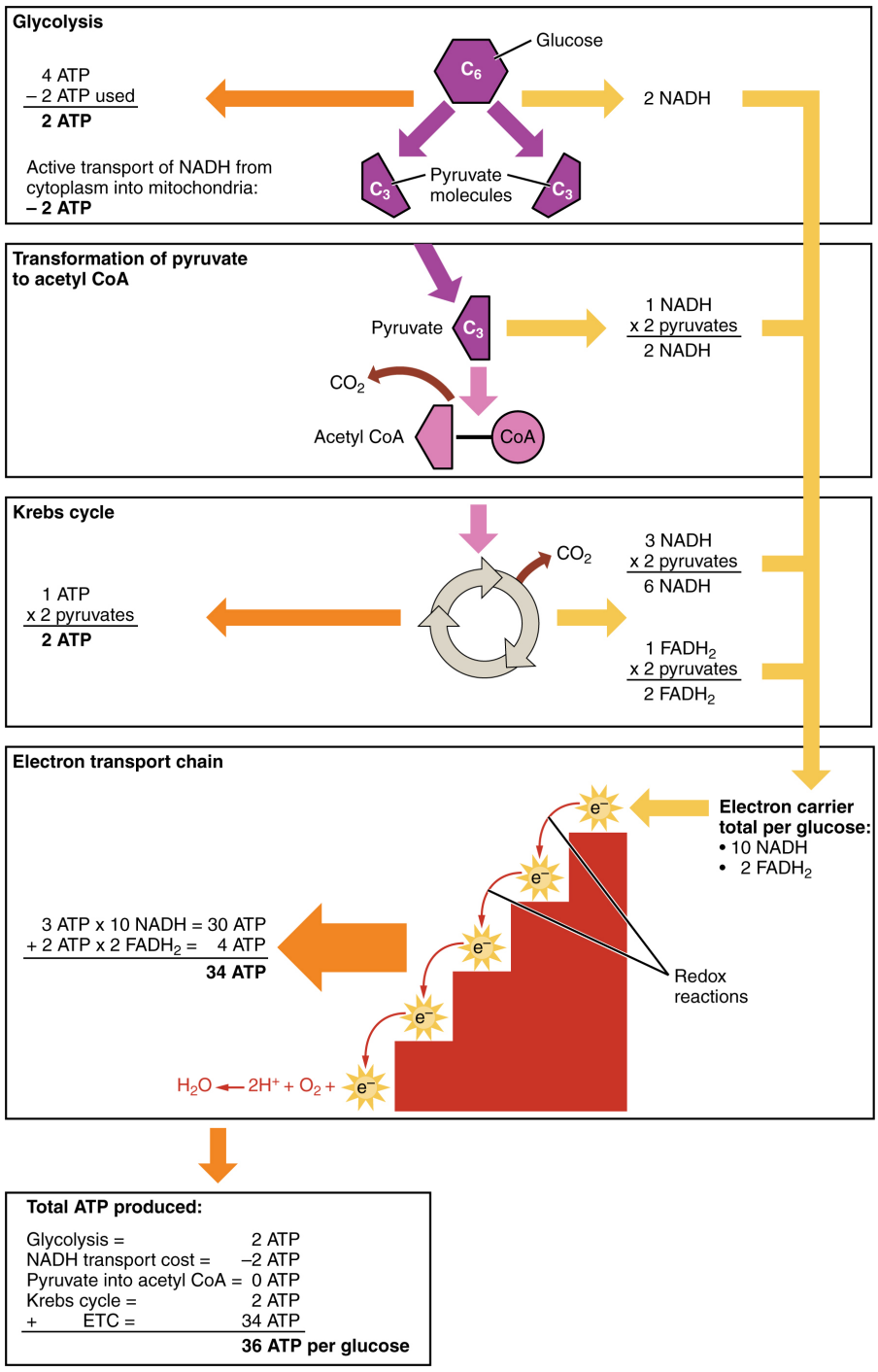


FIGURE 24.9 Carbohydrate Metabolism Carbohydrate metabolism involves glycolysis, the Krebs cycle, and the electron transport chain.

Gluconeogenesis

Gluconeogenesis is the synthesis of new glucose molecules from pyruvate, lactate, glycerol, or the amino acids alanine or glutamine. This process takes place primarily in the liver during periods of low glucose, that is, under conditions of fasting, starvation, and low carbohydrate diets. So, the question can be raised as to why the body would create something it has just spent a fair amount of effort to break down? Certain key organs, including the brain, can use only glucose as an energy source; therefore, it is essential that the body maintain a minimum blood glucose concentration. When the blood glucose concentration falls below that certain point, new glucose is synthesized by the liver to raise the blood concentration to normal.

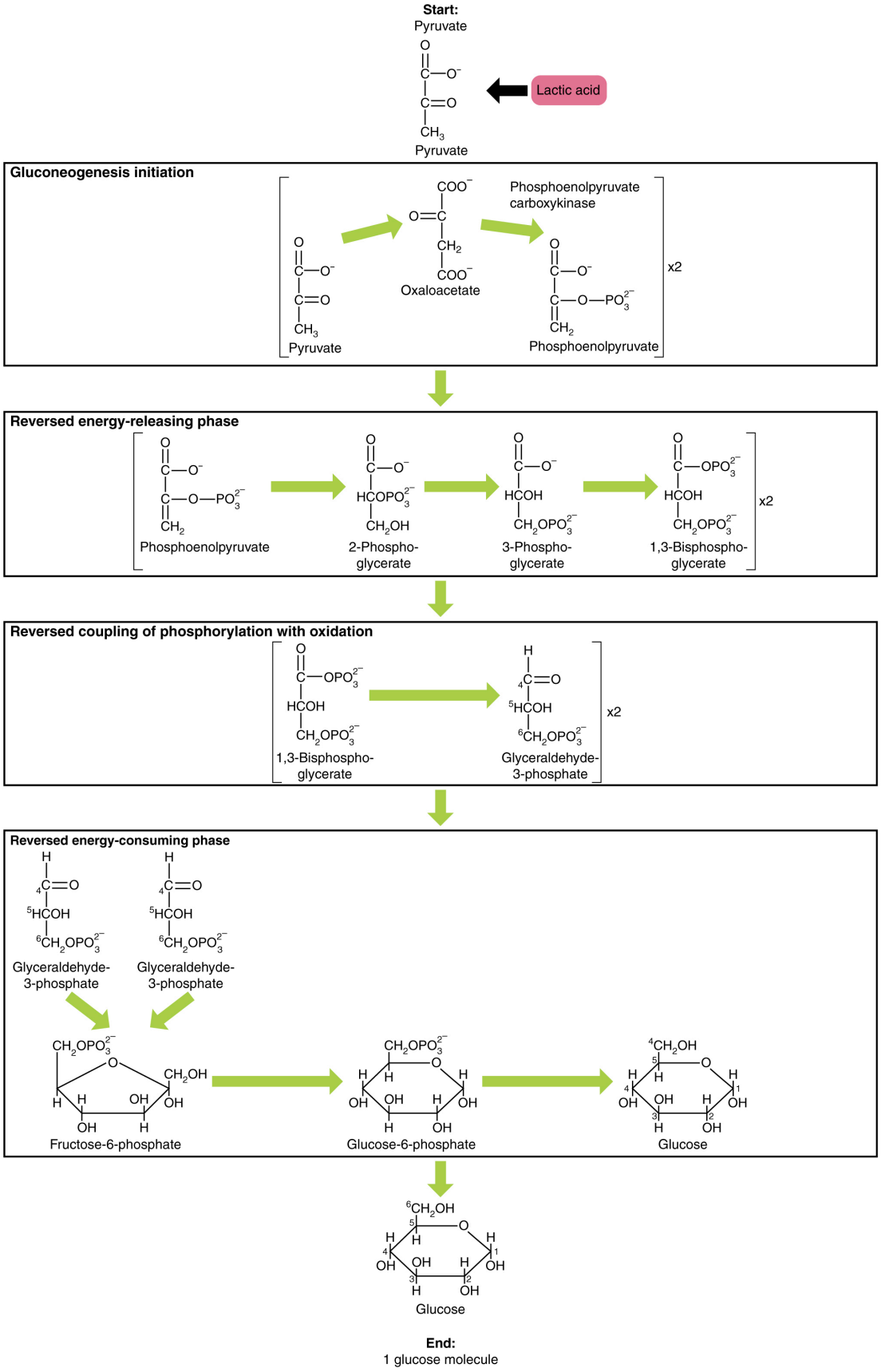


FIGURE 24.10 Gluconeogenesis Gluconeogenesis is the synthesis of glucose from pyruvate, lactate, glycerol, alanine, or glutamate.

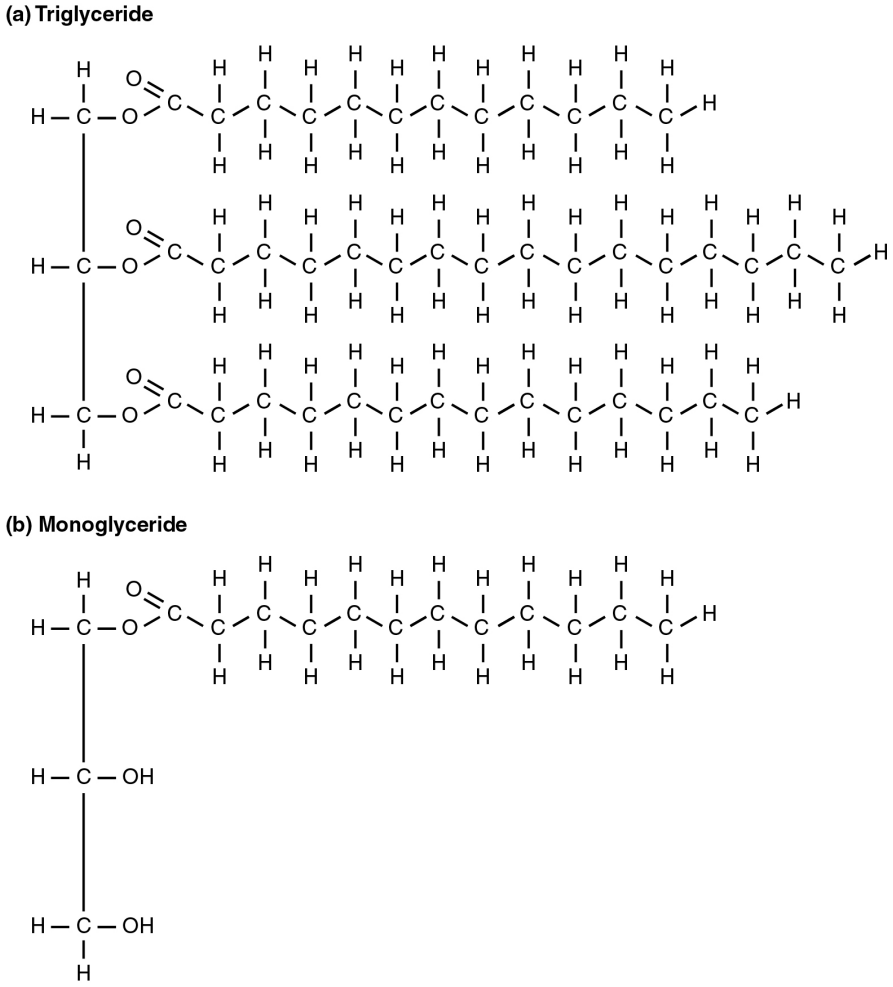


FIGURE 24.11 Triglyceride Broken Down into a Monoglyceride A triglyceride molecule (a) breaks down into a monoglyceride (b).

Lipid metabolism begins in the intestine where ingested **triglycerides** are broken down into smaller chain fatty acids and subsequently into **monoglyceride molecules** (see Figure 24.11**b**) by **pancreatic lipases**, enzymes that break down fats after they are emulsified by **bile salts**. When food reaches the small intestine in the form of chyme, a digestive hormone called **cholecystokinin (CCK)** is released by intestinal cells in the intestinal mucosa. CCK stimulates the release of pancreatic lipase from the pancreas and stimulates the contraction of the gallbladder to release stored bile salts into the intestine. CCK also travels to the brain, where it can act as a hunger suppressant.

Together, the pancreatic lipases and bile salts break down triglycerides into free fatty acids. These fatty acids can be transported across the intestinal membrane. However, once they cross the membrane, they are recombined to again form triglyceride molecules. Within the intestinal cells, these triglycerides are packaged along with cholesterol molecules in phospholipid vesicles called **chylomicrons** (Figure 24.12). The chylomicrons enable fats and cholesterol to move within the aqueous environment of your lymphatic and circulatory systems. Chylomicrons leave the enterocytes by exocytosis and enter the lymphatic system via lacteals in the villi of the intestine. From the lymphatic system, the chylomicrons are transported to the circulatory system. Once in the circulation, they can either go to the liver or be stored in fat cells (adipocytes) that comprise adipose (fat) tissue found throughout the body.

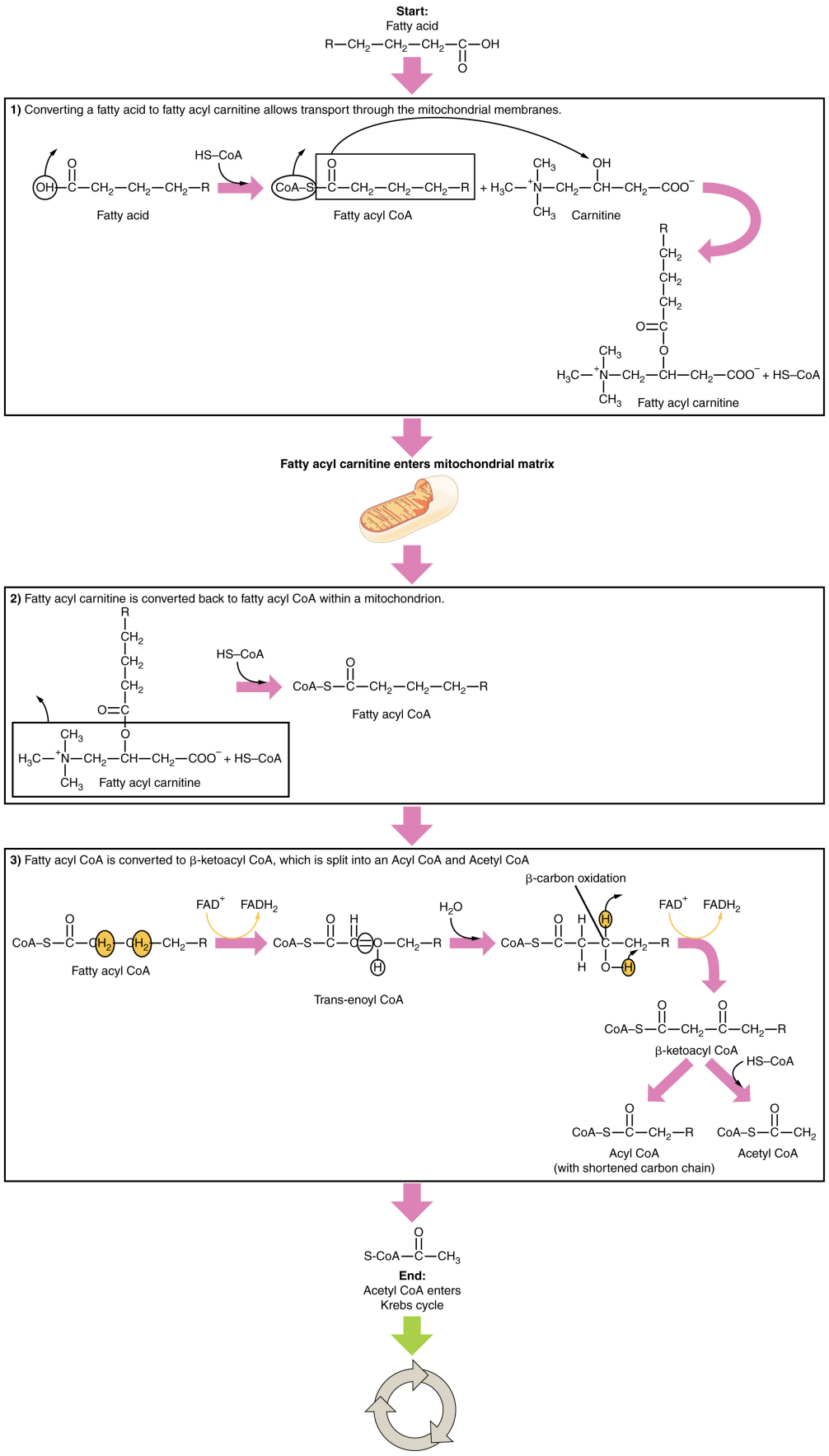


FIGURE 24.13 Breakdown of Fatty Acids During fatty acid oxidation, triglycerides can be broken down into acetyl CoA molecules and

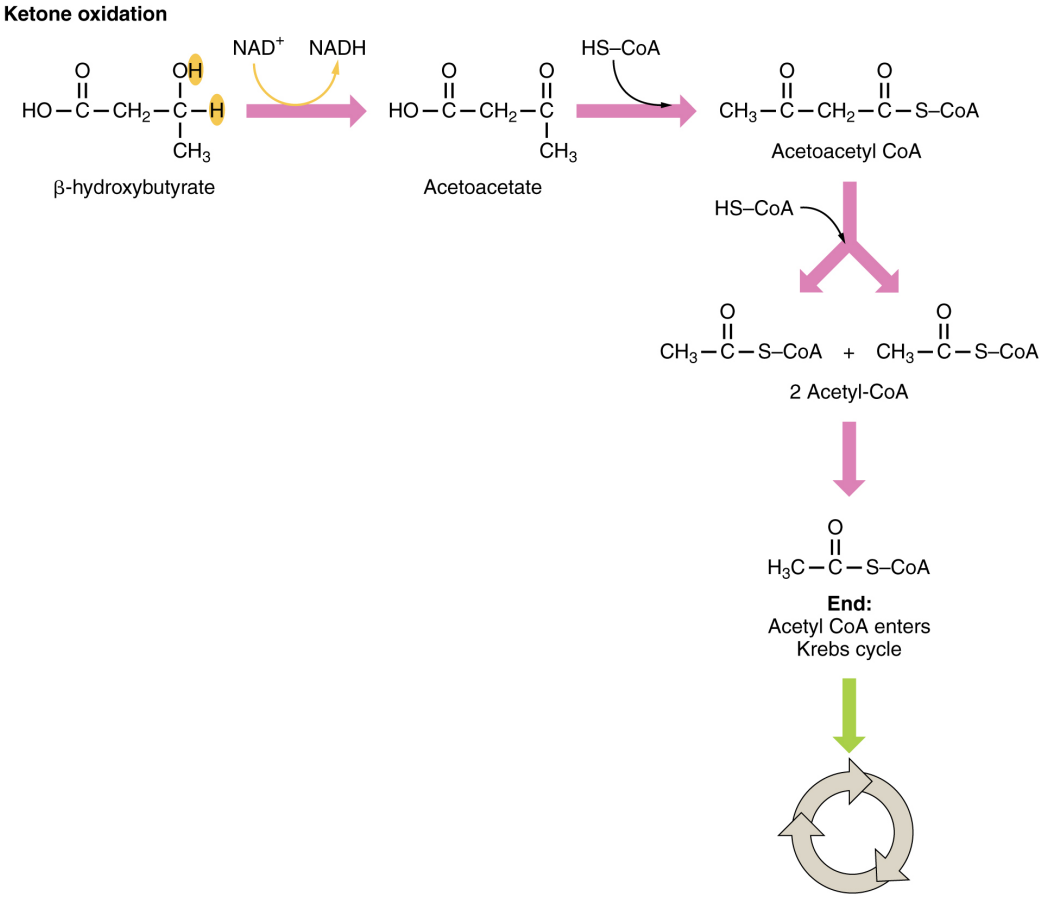


FIGURE 24.15 Ketone Oxidation When glucose is limited, ketone bodies can be oxidized to produce acetyl CoA to be used in the Krebs cycle to generate energy.

Lipogenesis

When glucose levels are plentiful, the excess acetyl CoA generated by glycolysis can be converted into fatty acids, triglycerides, cholesterol, steroids, and bile salts. This process, called **lipogenesis**, creates lipids (fat) from the acetyl CoA and takes place in the cytoplasm of adipocytes (fat cells) and hepatocytes (liver cells). When you eat more glucose or carbohydrates than your body needs, your system uses acetyl CoA to turn the excess into fat. Although there are several metabolic sources of acetyl CoA, it is most commonly derived from glycolysis. Acetyl CoA availability is significant, because it initiates lipogenesis. Lipogenesis begins with acetyl CoA and advances by the subsequent addition of two carbon atoms from another acetyl CoA; this process is repeated until fatty acids are the appropriate length. Because this is a bond-creating anabolic process, ATP is consumed. However, the creation of triglycerides and lipids is an efficient way of storing the energy available in carbohydrates. Triglycerides and lipids, high-energy molecules, are stored in adipose tissue until they are needed.

Although lipogenesis occurs in the cytoplasm, the necessary acetyl CoA is created in the mitochondria and cannot be transported across the mitochondrial membrane. To solve this problem, pyruvate is converted into both oxaloacetate and acetyl CoA. Two different enzymes are required for these conversions. Oxaloacetate forms via the action of pyruvate carboxylase, whereas the action of pyruvate dehydrogenase creates acetyl CoA. Oxaloacetate and acetyl CoA combine to form citrate, which can cross the mitochondrial membrane and enter the cytoplasm. In the cytoplasm, citrate is converted back into oxaloacetate and acetyl CoA. Oxaloacetate is converted into malate and then into pyruvate. Pyruvate crosses back across the mitochondrial membrane to wait for the next cycle of lipogenesis. The acetyl CoA is converted into malonyl CoA that is used to synthesize fatty acids. Figure 24.16 summarizes the pathways of lipid metabolism.

The digestion of proteins begins in the stomach. When protein-rich foods enter the stomach, they are greeted by a mixture of the enzyme **pepsin** and hydrochloric acid (HCl; 0.5 percent). The latter produces an environmental pH of 1.5–3.5 that denatures proteins within food. Pepsin cuts proteins into smaller polypeptides and their constituent amino acids. When the food-gastric juice mixture (chyme) enters the small intestine, the pancreas releases **sodium bicarbonate** to neutralize the HCl. This helps to protect the lining of the intestine. The small intestine also releases digestive hormones, including **secretin** and CCK, which stimulate digestive processes to break down the proteins further. Secretin also stimulates the pancreas to release sodium bicarbonate. The pancreas releases most of the digestive enzymes, including the proteases trypsin, chymotrypsin, and **elastase**, which aid protein digestion. Together, all of these enzymes break complex proteins into smaller individual amino acids (Figure 24.17), which are then transported across the intestinal mucosa to be used to create new proteins, or to be converted into fats or acetyl CoA and used in the Krebs cycle.

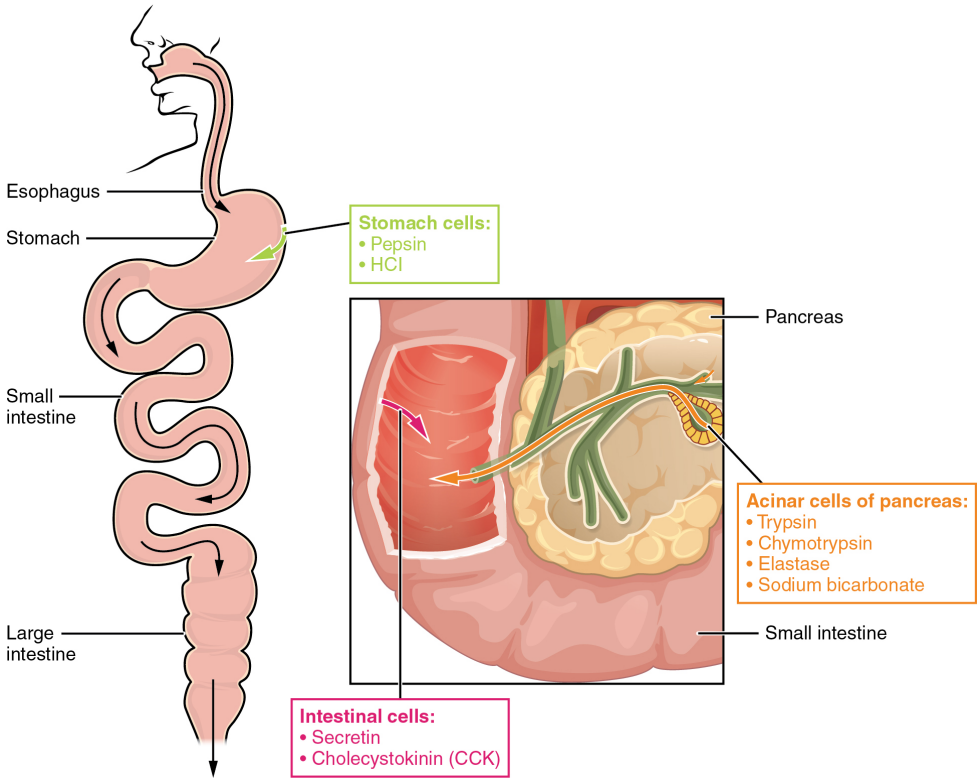


FIGURE 24.17 Digestive Enzymes and Hormones Enzymes in the stomach and small intestine break down proteins into amino acids. HCl in the stomach aids in proteolysis, and hormones secreted by intestinal cells direct the digestive processes.

In order to avoid breaking down the proteins that make up the pancreas and small intestine, pancreatic enzymes are released as **inactive proenzymes** that are only activated in the small intestine. In the pancreas, vesicles store **trypsin** and **chymotrypsin** as **trypsinogen** and **chymotrypsinogen**. Once released into the small intestine, an enzyme found in the wall of the small intestine, called **enterokinase**, binds to trypsinogen and converts it into its active form, trypsin. Trypsin then binds to chymotrypsinogen to convert it into the active chymotrypsin. Trypsin and chymotrypsin break down large proteins into smaller peptides, a process called **proteolysis**. These smaller peptides are catabolized into their constituent amino acids, which are transported across the apical surface of the intestinal mucosa in a process that is mediated by sodium-amino acid transporters. These transporters bind sodium and then bind the amino acid to transport it across the membrane. At the basal surface of the mucosal cells, the sodium and amino acid are released. The sodium can be reused in the transporter, whereas the amino acids are transferred into the bloodstream to be transported to the liver and cells throughout the body for protein synthesis.

Freely available amino acids are used to create proteins. If amino acids exist in excess, the body has no capacity or mechanism for their storage; thus, they are converted into glucose or ketones, or they are decomposed. Amino acid decomposition results in hydrocarbons and nitrogenous waste. However, high concentrations of nitrogenous byproducts are toxic. The urea cycle processes nitrogen and facilitates its excretion from the body.

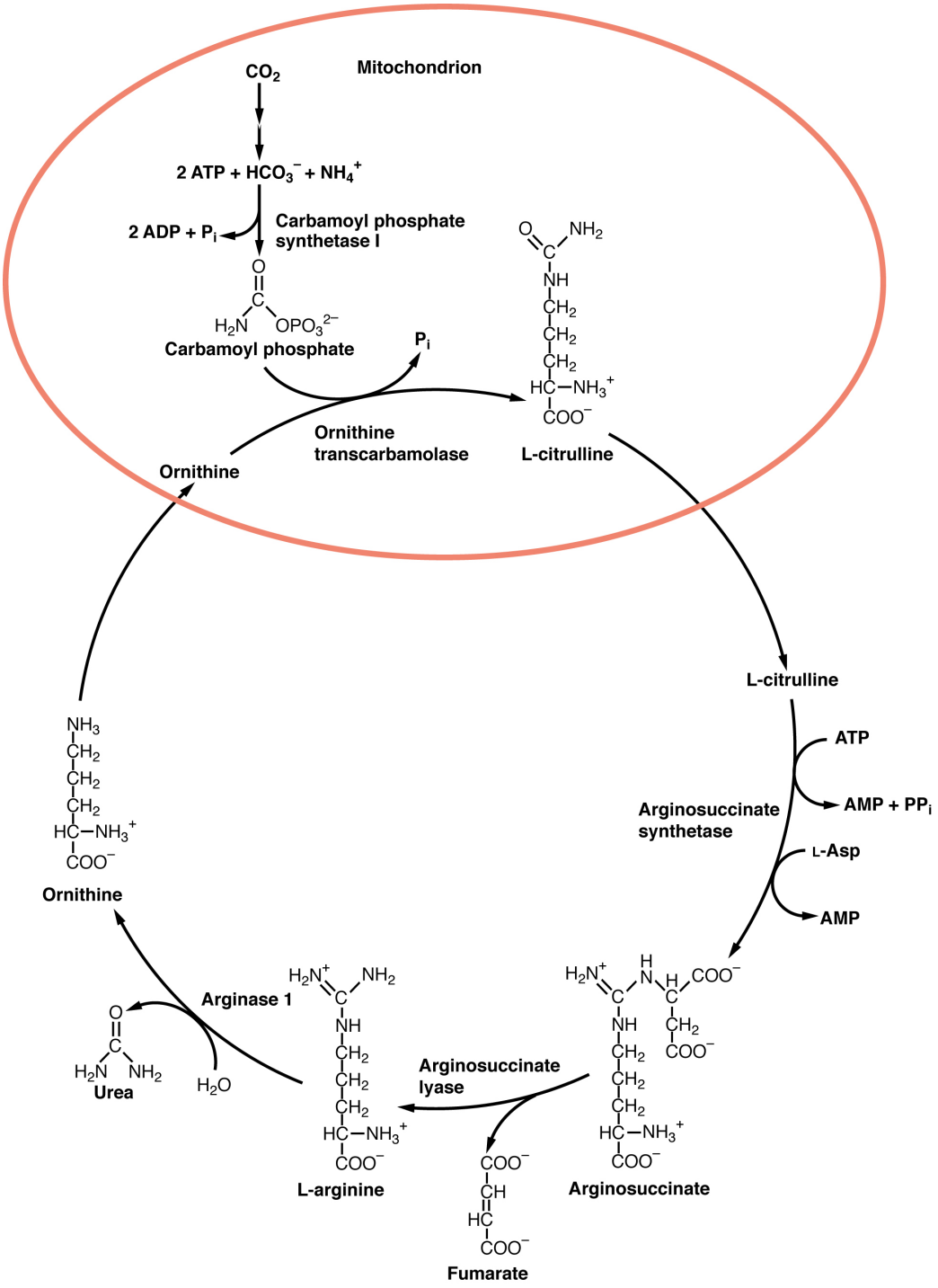


FIGURE 24.18 Urea Cycle Nitrogen is transaminated, creating ammonia and intermediates of the Krebs cycle. Ammonia is processed in the urea cycle to produce urea that is eliminated through the kidneys.

Amino acids can also be used as a source of energy, especially in times of starvation. Because the processing of amino acids results in the creation of metabolic intermediates, including pyruvate, acetyl CoA, acetoacyl CoA, oxaloacetate, and α-ketoglutarate, amino acids can serve as a source of energy production through the Krebs cycle (Figure 24.19). Figure 24.20 summarizes the pathways of catabolism and anabolism for carbohydrates, lipids, and proteins.

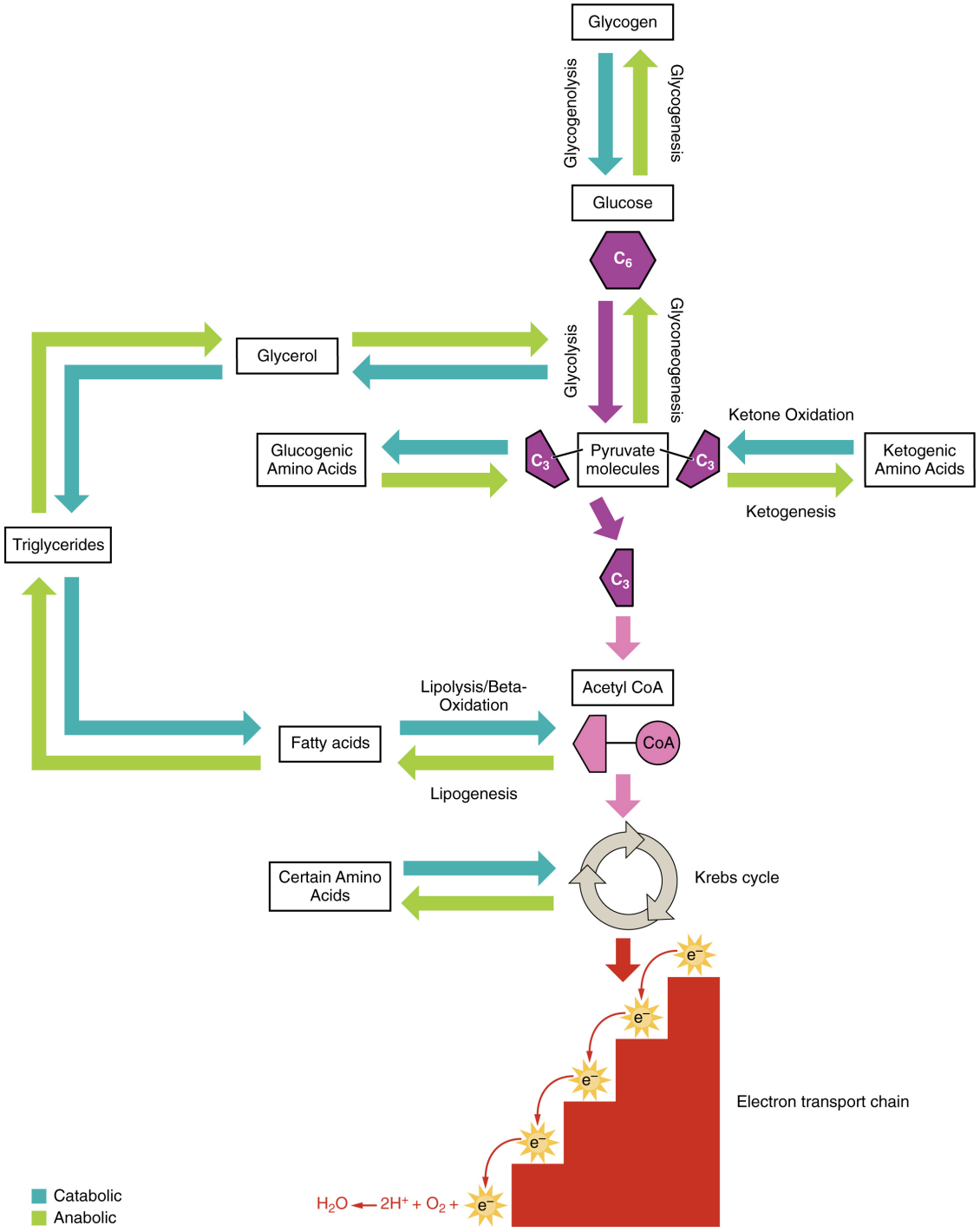


FIGURE 24.20 Catabolic and Anabolic Pathways Nutrients follow a complex pathway from ingestion through anabolism and catabolism to energy production.

Disorders of the...

Metabolism: Pyruvate Dehydrogenase Complex Deficiency and Phenylketonuria

Pyruvate dehydrogenase complex deficiency (PDCD) and phenylketonuria (PKU) are genetic disorders. Pyruvate dehydrogenase is the enzyme that converts pyruvate into acetyl CoA, the molecule necessary to begin the Krebs cycle to produce ATP. With low levels of the pyruvate dehydrogenase complex (PDC), the rate of cycling through the Krebs cycle is dramatically reduced. This results in a decrease in the total amount of energy that is produced by the cells of the body. PDC deficiency results in a neurodegenerative disease that ranges in severity,

Figure 24.21 summarizes the metabolic processes occurring in the body during the absorptive state.

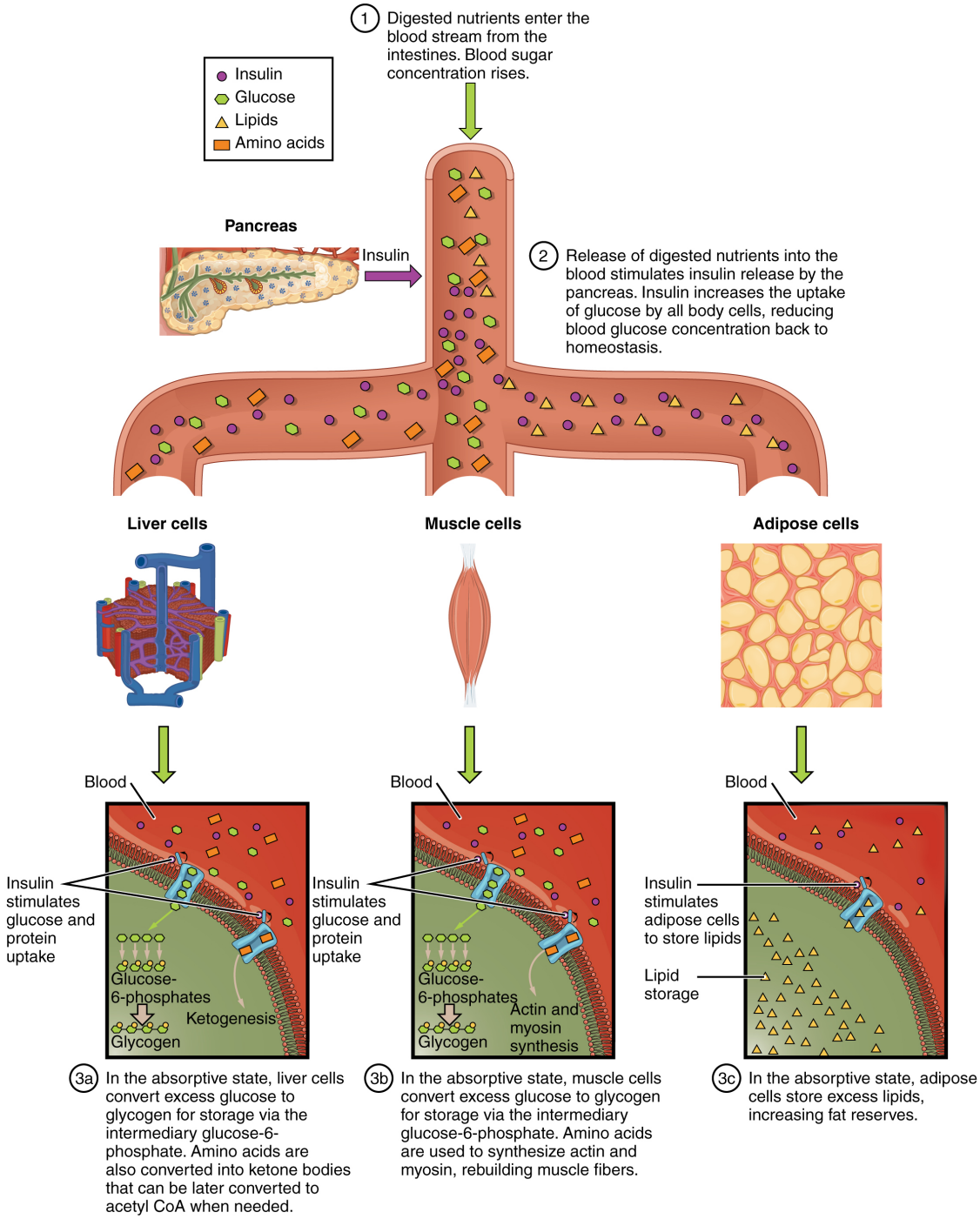


FIGURE 24.21 Absorptive State During the absorptive state, the body digests food and absorbs the nutrients.

The Postabsorptive State

The **postabsorptive state**, or the fasting state, occurs when the food has been digested, absorbed, and stored. You commonly fast overnight, but skipping meals during the day puts your body in the postabsorptive state as well. During this state, the body must rely initially on stored **glycogen**. Glucose levels in the blood begin to drop as it is absorbed and used by the cells. In response to the decrease in glucose, insulin levels also drop. Glycogen and triglyceride storage slows. However, due to the demands of the tissues and organs, blood glucose levels must be maintained in the normal range of 80–120 mg/dL. In response to a drop in blood glucose concentration, the hormone glucagon is released from the alpha cells of the pancreas. Glucagon acts upon the liver cells, where it

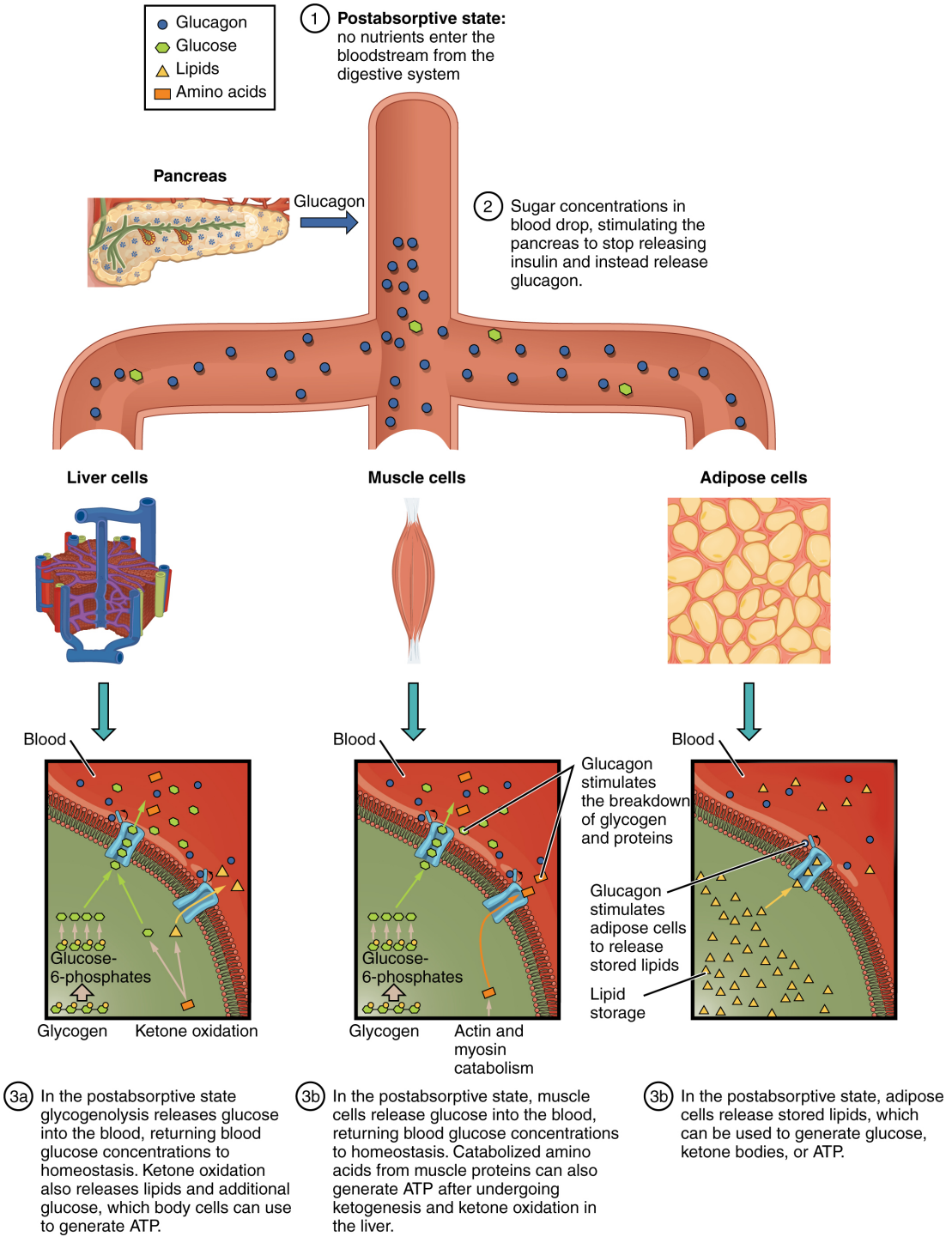


FIGURE 24.22 Postabsorptive State During the postabsorptive state, the body must rely on stored glycogen for energy.

Starvation

When the body is deprived of nourishment for an extended period of time, it goes into "survival mode." The first priority for survival is to provide enough glucose or fuel for the brain. The second priority is the conservation of amino acids for proteins. Therefore, the body uses ketones to satisfy the energy needs of the brain and other glucose-dependent organs, and to maintain proteins in the cells (see Figure 24.2). Because glucose levels are very low during starvation, glycolysis will shut off in cells that can use alternative fuels. For example, muscles will switch from using glucose to fatty acids as fuel. As previously explained, fatty acids can be converted into acetyl CoA and processed through the Krebs cycle to make ATP. Pyruvate, lactate, and alanine from muscle cells are not converted

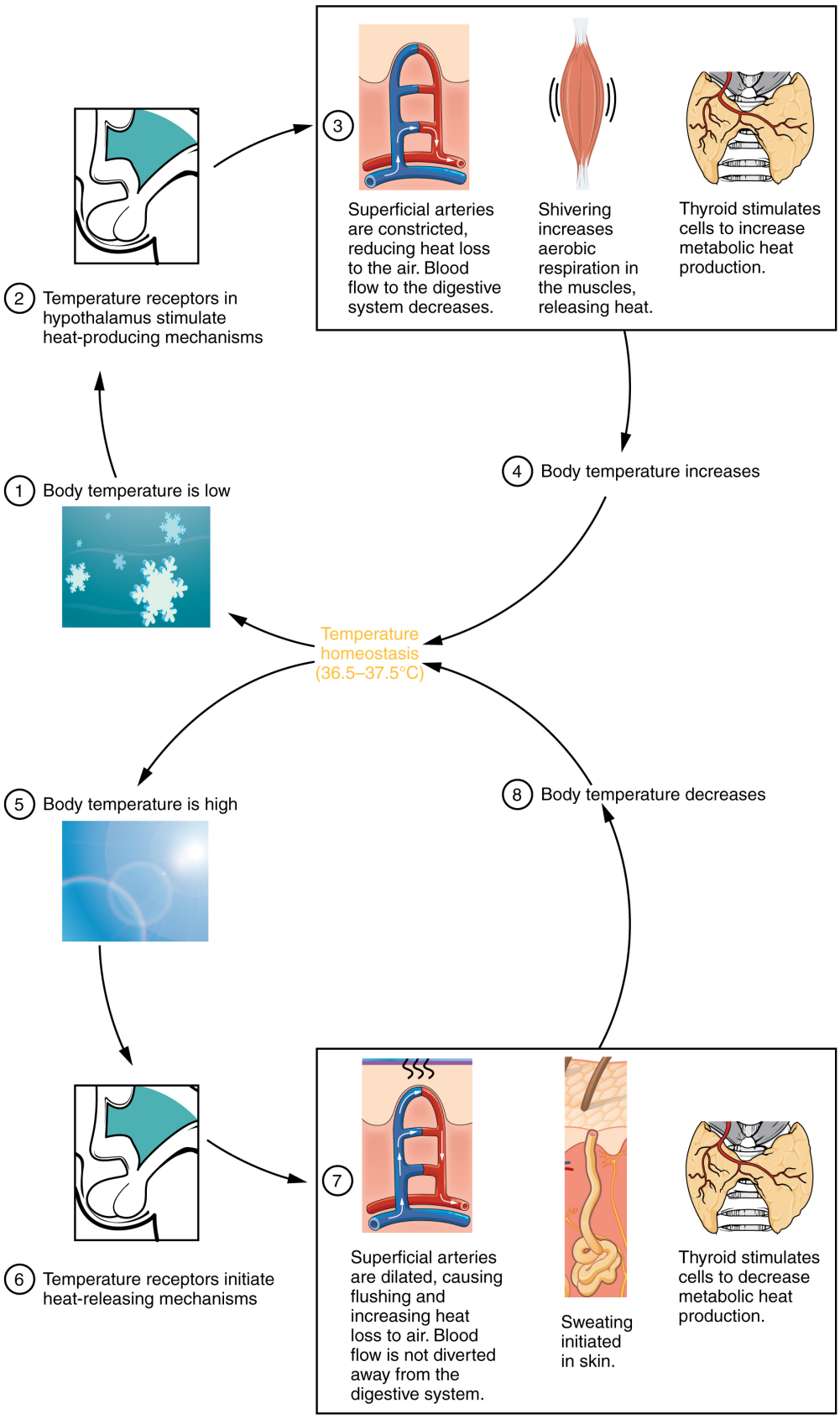


FIGURE 24.23 Hypothalamus Controls Thermoregulation The hypothalamus controls thermoregulation.

amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C. This is different from the calorie (c) used in the physical sciences, which is the amount of heat it takes to raise 1 g of water by 1 °C. When we refer to "calorie," we are referring to the nutritional Calorie.

On average, a person needs 1500 to 2000 calories per day to sustain (or carry out) daily activities. The total number of calories needed by one person is dependent on their body mass, age, height, gender, activity level, and the amount of exercise per day. If exercise is regular part of one's day, more calories are required. As a rule, people underestimate the number of calories ingested and overestimate the amount they burn through exercise. This can lead to ingestion of too many calories per day. The accumulation of an extra 3500 calories adds one pound of weight. If an excess of 200 calories per day is ingested, one extra pound of body weight will be gained every 18 days. At that rate, an extra 20 pounds can be gained over the course of a year. Of course, this increase in calories could be offset by increased exercise. Running or jogging one mile burns almost 100 calories.

The type of food ingested also affects the body's metabolic rate. Processing of carbohydrates requires less energy than processing of proteins. In fact, the breakdown of carbohydrates requires the least amount of energy, whereas the processing of proteins demands the most energy. In general, the amount of calories ingested and the amount of calories burned determines the overall weight. To lose weight, the number of calories burned per day must exceed the number ingested. Calories are in almost everything you ingest, so when considering calorie intake, beverages must also be considered.

To help provide guidelines regarding the types and quantities of food that should be eaten every day, the USDA has updated their food guidelines from MyPyramid to MyPlate. They have put the recommended elements of a healthy meal into the context of a place setting of food. MyPlate categorizes food into the standard six food groups: fruits, vegetables, grains, protein foods, dairy, and oils. The accompanying website gives clear recommendations regarding quantity and type of each food that you should consume each day, as well as identifying which foods belong in each category. The accompanying graphic (Figure 24.24) gives a clear visual with general recommendations for a healthy and balanced meal. The guidelines recommend to "Make half your plate fruits and vegetables." The other half is grains and protein, with a slightly higher quantity of grains than protein. Dairy products are represented by a drink, but the quantity can be applied to other dairy products as well.

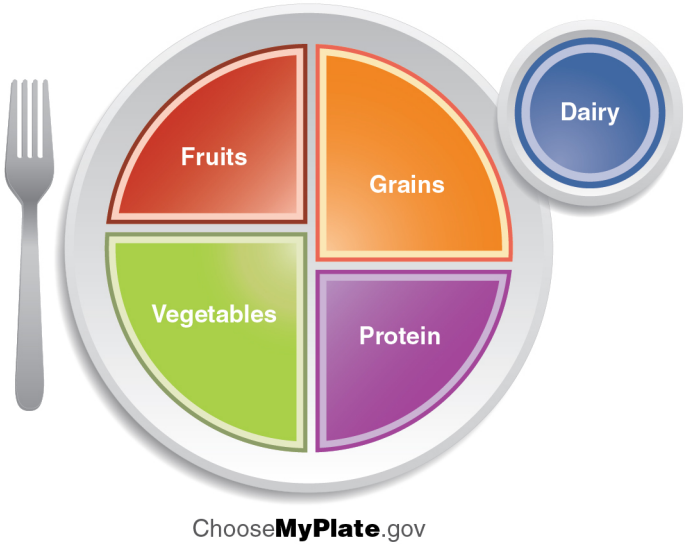


FIGURE 24.24 MyPlate The U.S. Department of Agriculture developed food guidelines called MyPlate to help demonstrate how to maintain a healthy lifestyle.

ChooseMyPlate.gov provides extensive online resources for planning a healthy diet and lifestyle, including offering weight management tips and recommendations for physical activity. It also includes the SuperTracker, a web-based application to help you analyze your own diet and physical activity.

Fat-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
A retinal or β-carotene	Yellow and orange fruits and vegetables, dark green leafy vegetables, eggs, milk, liver	700–900 μg	Eye and bone development, immune function	Night blindness, epithelial changes, immune system deficiency
D cholecalciferol	Dairy products, egg yolks; also synthesized in the skin from exposure to sunlight	5–15 μg	Aids in calcium absorption, promoting bone growth	Rickets, bone pain, muscle weakness, increased risk of death from cardiovascular disease, cognitive impairment, asthma in children, cancer
E tocopherols	Seeds, nuts, vegetable oils, avocados, wheat germ	15 mg	Antioxidant	Anemia
K phylloquinone	Dark green leafy vegetables, broccoli, Brussels sprouts, cabbage	90–120 μg	Blood clotting, bone health	Hemorrhagic disease of newborn in infants; uncommon in adults

TABLE 24.3

Water-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B_1 thiamine	Whole grains, enriched bread and cereals, milk, meat	1.1–1.2 mg	Carbohydrate metabolism	Beriberi, Wernicke-Korsakoff syndrome
B_2 riboflavin	Brewer's yeast, almonds, milk, organ meats, legumes, enriched breads and cereals, broccoli, asparagus	1.1–1.3 mg	Synthesis of FAD for metabolism, production of red blood cells	Fatigue, slowed growth, digestive problems, light sensitivity, epithelial problems like cracks in the corners of the mouth

TABLE 24.4

quantities: potassium, sodium, calcium, phosphorus, magnesium, and chloride.

The most common minerals in the body are calcium and phosphorous, both of which are stored in the skeleton and necessary for the hardening of bones. Most minerals are ionized, and their ionic forms are used in physiological processes throughout the body. Sodium and chloride ions are electrolytes in the blood and extracellular tissues, and iron ions are critical to the formation of hemoglobin. There are additional trace minerals that are still important to the body's functions, but their required quantities are much lower.

Like vitamins, minerals can be consumed in toxic quantities (although it is rare). A healthy diet includes most of the minerals your body requires, so supplements and processed foods can add potentially toxic levels of minerals. Table 24.5 and Table 24.6 provide a summary of minerals and their function in the body.

Major Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Potassium	Meats, some fish, fruits, vegetables, legumes, dairy products	4700 mg	Nerve and muscle function; acts as an electrolyte	Hypokalemia: weakness, fatigue, muscle cramping, gastrointestinal problems, cardiac problems
Sodium	Table salt, milk, beets, celery, processed foods	2300 mg	Blood pressure, blood volume, muscle and nerve function	Rare
Calcium	Dairy products, dark green leafy vegetables, blackstrap molasses, nuts, brewer's yeast, some fish	1000 mg	Bone structure and health; nerve and muscle functions, especially cardiac function	Slow growth, weak and brittle bones
Phosphorous	Meat, milk	700 mg	Bone formation, metabolism, ATP production	Rare
Magnesium	Whole grains, nuts, leafy green vegetables	310–420 mg	Enzyme activation, production of energy, regulation of other nutrients	Agitation, anxiety, sleep problems, nausea and vomiting, abnormal heart rhythms, low blood pressure, muscular problems
Chloride	Most foods, salt, vegetables, especially seaweed, tomatoes, lettuce, celery, olives	2300 mg	Balance of body fluids, digestion	Loss of appetite, muscle cramps

TABLE 24.5

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Selenium	Brewer's yeast, wheat germ, liver, butter, fish, shellfish, whole grains	55 μg	Antioxidant, thyroid function, immune system function	Muscle pain
Chromium	Whole grains, lean meats, cheese, black pepper, thyme, brewer's yeast	25–35 μg	Insulin function	High blood sugar, triglyceride, and cholesterol levels
Molybdenum	Legumes, whole grains, nuts	45 μg	Cofactor for enzymes	Rare

TABLE 24.6

the amount of energy expended by the body

metabolism sum of all catabolic and anabolic reactions that take place in the body

minerals inorganic compounds required by the body to ensure proper function of the body

monoglyceride molecules lipid consisting of a single fatty acid chain attached to a glycerol backbone

monosaccharide smallest, monomeric sugar molecule

NADH high-energy molecule needed for glycolysis

nicotinamide adenine dinucleotide (NAD) coenzyme used to produce NADH

oxidation loss of an electron

oxidation-reduction reaction (also, redox reaction) pair of reactions in which an electron is passed from one molecule to another, oxidizing one and reducing the other

oxidative phosphorylation process that converts high-energy NADH and $FADH_2$ into ATP

pancreatic lipases enzymes released from the pancreas that digest lipids in the diet

pepsin enzyme that begins to break down proteins in the stomach

polysaccharides complex carbohydrates made up of many monosaccharides

postabsorptive state also called the fasting state; the metabolic state occurring after digestion when food is no longer the body's source of energy and it must rely on stored glycogen

proteolysis process of breaking proteins into smaller peptides

pyruvate three-carbon end product of glycolysis and starting material that is converted into acetyl CoA that enters the Krebs cycle

radiation transfer of heat via infrared waves

reduction gaining of an electron

salivary amylase digestive enzyme that is found in the saliva and begins the digestion of carbohydrates in the mouth

secretin hormone released in the small intestine to aid in digestion

sodium bicarbonate anion released into the small intestine to neutralize the pH of the food from the stomach

terminal electron acceptor oxygen, the recipient of the free hydrogen at the end of the electron transport chain

thermoneutral external temperature at which the body does not expend any energy for thermoregulation, about 84 °F

thermoregulation process of regulating the temperature of the body

transamination transfer of an amine group from one molecule to another as a way to turn nitrogen waste into ammonia so that it can enter the urea cycle

tricarboxylic acid cycle (TCA) also called the Krebs cycle or the citric acid cycle; converts pyruvate into CO_2 and high-energy $FADH_2$, NADH, and ATP molecules

triglycerides lipids, or fats, consisting of three fatty acid chains attached to a glycerol backbone

trypsin pancreatic enzyme that activates chymotrypsin and digests protein

trypsinogen proenzyme form of trypsin

urea cycle process that converts potentially toxic nitrogen waste into urea that can be eliminated through the kidneys

vitamins organic compounds required by the body to perform biochemical reactions like metabolism and bone, cell, and tissue growth

Chapter Review

24.1 Overview of Metabolic Reactions

Metabolism is the sum of all catabolic (break down) and anabolic (synthesis) reactions in the body. The metabolic rate measures the amount of energy used to maintain life. An organism must ingest a sufficient amount of food to maintain its metabolic rate if the organism is to stay alive for very long.

Catabolic reactions break down larger molecules, such as carbohydrates, lipids, and proteins from ingested food, into their constituent smaller parts. They also include the breakdown of ATP, which releases the energy needed for metabolic processes in all cells throughout the body.

Anabolic reactions, or biosynthetic reactions, synthesize larger molecules from smaller constituent parts, using ATP as the energy source for these reactions. Anabolic reactions build bone, muscle mass, and new proteins, fats, and nucleic acids. Oxidation-reduction reactions transfer electrons across molecules by oxidizing one molecule and reducing another, and collecting the released energy to convert P_i and ADP into ATP. Errors in metabolism alter the processing of carbohydrates, lipids, proteins, and nucleic acids, and can result in a number of disease states.

24.2 Carbohydrate Metabolism

Metabolic enzymes catalyze catabolic reactions that break down carbohydrates contained in food. The energy released is used to power the cells and systems that make up your body. Excess or unutilized energy is

its breakdown into glucose. The glucose is released into the bloodstream to serve as a fuel source for cells throughout the body. If glycogen stores are depleted during fasting, alternative sources, including fatty acids and proteins, can be metabolized and used as fuel. When the body once again enters the absorptive state after fasting, fats and proteins are digested and used to replenish fat and protein stores, whereas glucose is processed and used first to replenish the glycogen stores in the peripheral tissues, then in the liver. If the fast is not broken and starvation begins to set in, during the initial days, glucose produced from gluconeogenesis is still used by the brain and organs. After a few days, however, ketone bodies are created from fats and serve as the preferential fuel source for the heart and other organs, so that the brain can still use glucose. Once these stores are depleted, proteins will be catabolized first from the organs with fast turnover, such as the intestinal lining. Muscle will be spared to prevent the wasting of muscle tissue; however, these proteins will be used if alternative stores are not available.

24.6 Energy and Heat Balance

Some of the energy from the food that is ingested is used to maintain the core temperature of the body. Most of the energy derived from the food is released as heat. The core temperature is kept around 36.5–37.5 °C (97.7–99.5 °F). This is tightly regulated by the hypothalamus in the brain, which senses changes in the core temperature and operates like a thermostat to increase sweating or shivering, or inducing other mechanisms to return the temperature to its normal range. The body can also gain or lose heat through mechanisms of heat exchange. Conduction transfers heat from one object to another through physical contact. Convection transfers heat to air or water. Radiation transfers heat via infrared radiation. Evaporation transfers heat as water changes state from a liquid to a gas.

24.7 Nutrition and Diet

Nutrition and diet affect your metabolism. More energy is required to break down fats and proteins than carbohydrates; however, all excess calories that are ingested will be stored as fat in the body. On average, a person requires 1500 to 2000 calories for normal daily activity, although routine exercise will increase that amount. If you ingest more than that, the remainder is stored for later use. Conversely, if you ingest less than that, the energy stores in your body will be depleted. Both the quantity and quality of the food you eat affect your metabolism and can affect your overall health. Eating too much or too little can result in serious medical conditions, including cardiovascular disease, cancer, and diabetes.

Vitamins and minerals are essential parts of the diet. They are needed for the proper function of metabolic pathways in the body. Vitamins are not stored in the body, so they must be obtained from the diet or synthesized from precursors available in the diet. Minerals are also obtained from the diet, but they are also stored, primarily in skeletal tissues.

Review Questions

1. A monosaccharide is formed from a polysaccharide in what kind of reaction?
   a. oxidation–reduction reaction
   b. anabolic reaction
   c. catabolic reaction
   d. biosynthetic reaction

2. If anabolic reactions exceed catabolic reactions, the result will be _____.
   a. weight loss
   b. weight gain
   c. metabolic rate change
   d. development of disease

3. When NAD becomes NADH, the coenzyme has been _____.
   a. reduced
   b. oxidized
   c. metabolized
   d. hydrolyzed

4. Anabolic reactions use energy by _____.
   a. turning ADP into ATP
   b. removing a phosphate group from ATP
   c. producing heat
   d. breaking down molecules into smaller parts

5. Glycolysis results in the production of two _____ molecules from a single molecule of glucose. In the absence of _____, the end product of glycolysis is _____.
   a. acetyl CoA, pyruvate, lactate
   b. ATP, carbon, pyruvate
   c. pyruvate, oxygen, lactate
   d. pyruvate, carbon, acetyl CoA

21. The postabsorptive state relies on stores of _____ in the _____.
a. insulin; pancreas
b. glucagon; pancreas
c. glycogen; liver
d. glucose; liver

22. The body's temperature is controlled by the _____. This temperature is always kept between _____.
a. pituitary; 36.5–37.5 °C
b. hypothalamus; 97.7–99.5 °F
c. hypothalamus; 36.5–37.5 °F
d. pituitary; 97.7–99.5 °F

23. Fever increases the body temperature and can induce chills to help cool the temperature back down. What other mechanisms are in place to regulate the body temperature?
a. shivering
b. sweating
c. erection of the hairs on the arms and legs
d. all of the above

24. The heat you feel on your chair when you stand up was transferred from your skin via _____.
a. conduction
b. convection
c. radiation
d. evaporation

25. A crowded room warms up through the mechanism of _____.
a. conduction
b. convection
c. radiation
d. evaporation

26. A deficiency in vitamin A can result in _____.
a. improper bone development
b. scurvy
c. improper eye development or sight
d. all of the above

27. Rickets results in improper bone development in children that arises from the malabsorption of calcium and a deficiency in _____.
a. vitamin D
b. vitamin C
c. vitamin B_{12}
d. niacin

28. Consuming which type of food will help the most with weight loss?
a. fats
b. vegetables
c. lean meats
d. fruits

29. Which of the following is stored in the body?
a. thiamine
b. phosphorous
c. folic acid
d. vitamin C

Critical Thinking Questions

30. Describe how metabolism can be altered.
31. Describe how Addison's disease can be treated.
32. Explain how glucose is metabolized to yield ATP.
33. Insulin is released when food is ingested and stimulates the uptake of glucose into the cell. Discuss the mechanism cells employ to create a concentration gradient to ensure continual uptake of glucose from the bloodstream.
34. Discuss how carbohydrates can be stored as fat.
35. If a person with diabetes that has breath smells like alcohol, what could this mean?
36. Amino acids are not stored in the body. Describe how excess amino acids are processed in the cell.
37. Release of trypsin and chymotrypsin in their active form can result in the digestion of the pancreas or small intestine itself. What mechanism does the body employ to prevent its self-destruction?
38. In type II diabetes, insulin is produced but is nonfunctional. These patients are described as "starving in a sea of plenty," because their blood glucose levels are high, but none of the glucose is transported into the cells. Describe how this leads to malnutrition.
39. Ketone bodies are used as an alternative source of fuel during starvation. Describe how ketones are synthesized.
40. How does vasoconstriction help increase the core temperature of the body?
41. How can the ingestion of food increase the body temperature?
42. Weight loss and weight gain are complex processes. What are some of the main factors that influence weight gain in people?

convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: "What happens if this does not work?" This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one's life.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/urineintro) from the Howard Hughes Medical Institute for an introduction to the urinary system.

25.1 Physical Characteristics of Urine

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors (Table 25.1). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Normal Urine Characteristics

Characteristic	Normal values
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032

TABLE 25.1

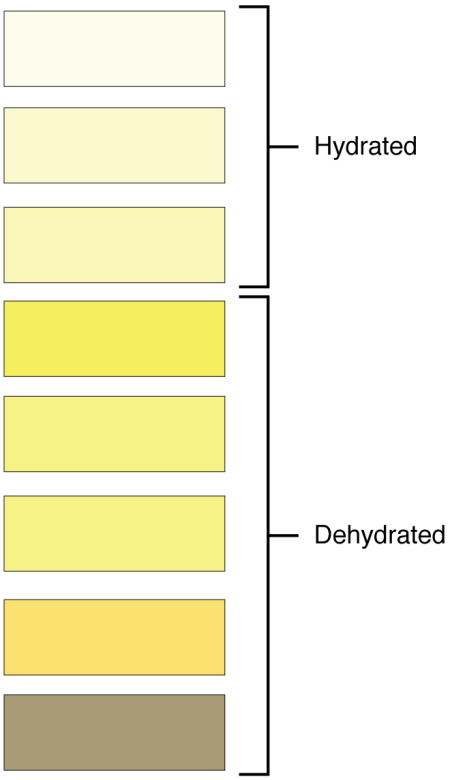


FIGURE 25.2 **Urine Color**

Urine volume varies considerably. The normal range is one to two liters per day (Table 25.2). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Urine Volumes

Volume condition	Volume	Causes
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake

TABLE 25.2

and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical (Figure 25.3).

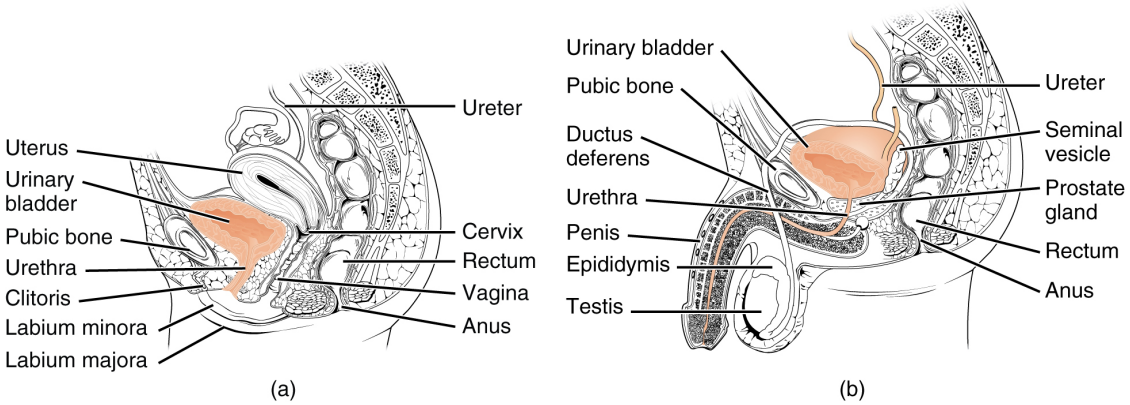


FIGURE 25.3 Female and Male Urethras The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.

The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the **trigone** (Greek tri- = "triangle" and the root of the word "trigonometry"). The urethra tracks posterior and inferior to the pubic symphysis (see Figure 25.3**a**). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled **internal urinary sphincter**, consisting of smooth muscle and voluntary skeletal muscle that forms the **external urinary sphincter** below it.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in females. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see Figure 25.3**b**). The length of the male urethra varies between people but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper's glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal (Figure 25.5). Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the **sacral micturition center**. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

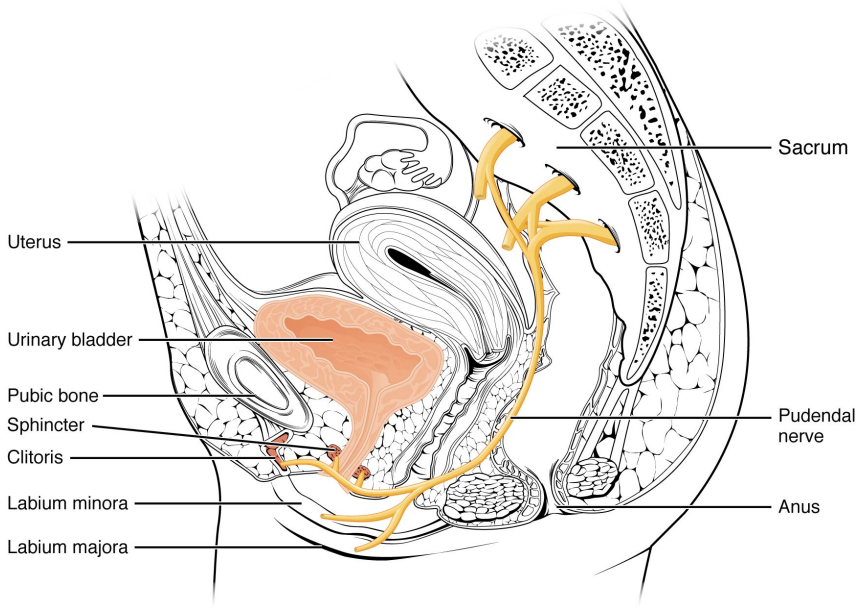


FIGURE 25.5 **Nerves Innervating the Urinary System**

Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates a one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium (Figure 25.6) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.

called the **renal fat pad**, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

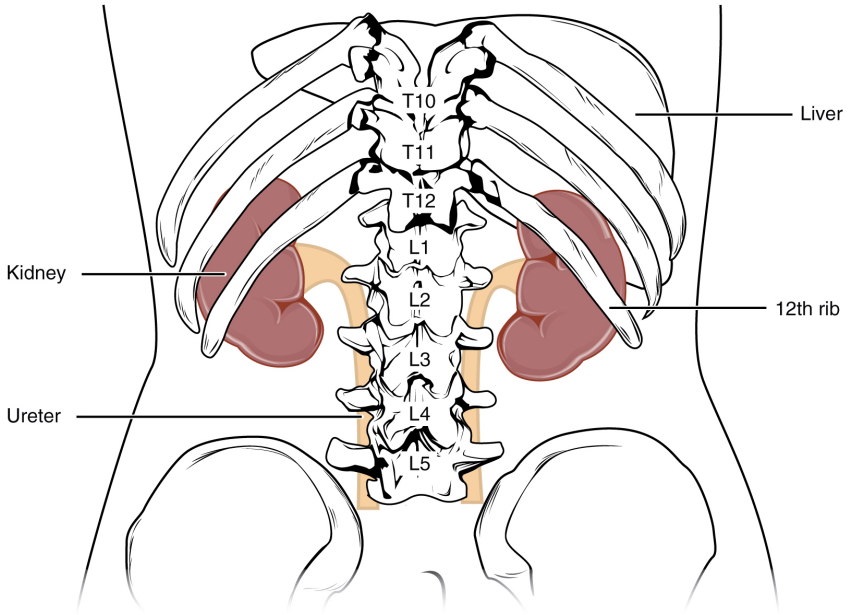


FIGURE 25.7 **Kidneys** The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** (Figure 25.8). The **renal columns** are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

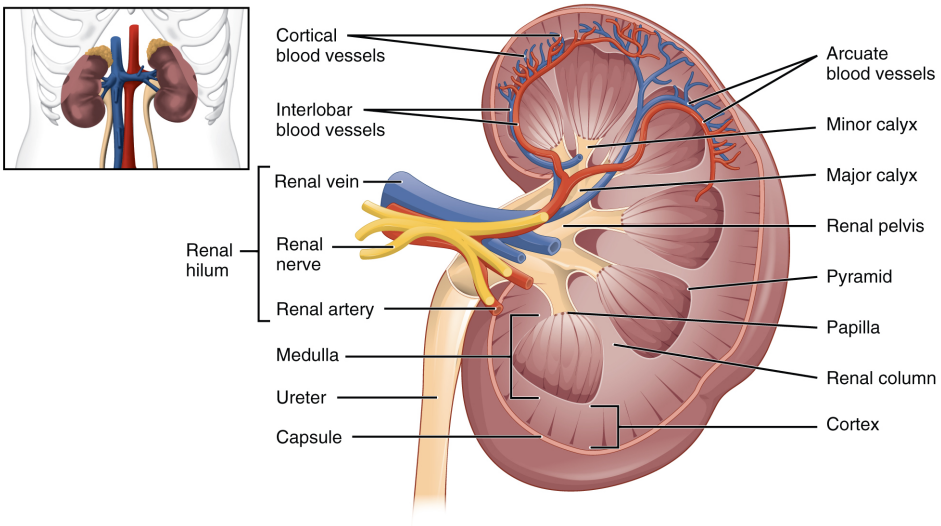


FIGURE 25.8 **Left Kidney**

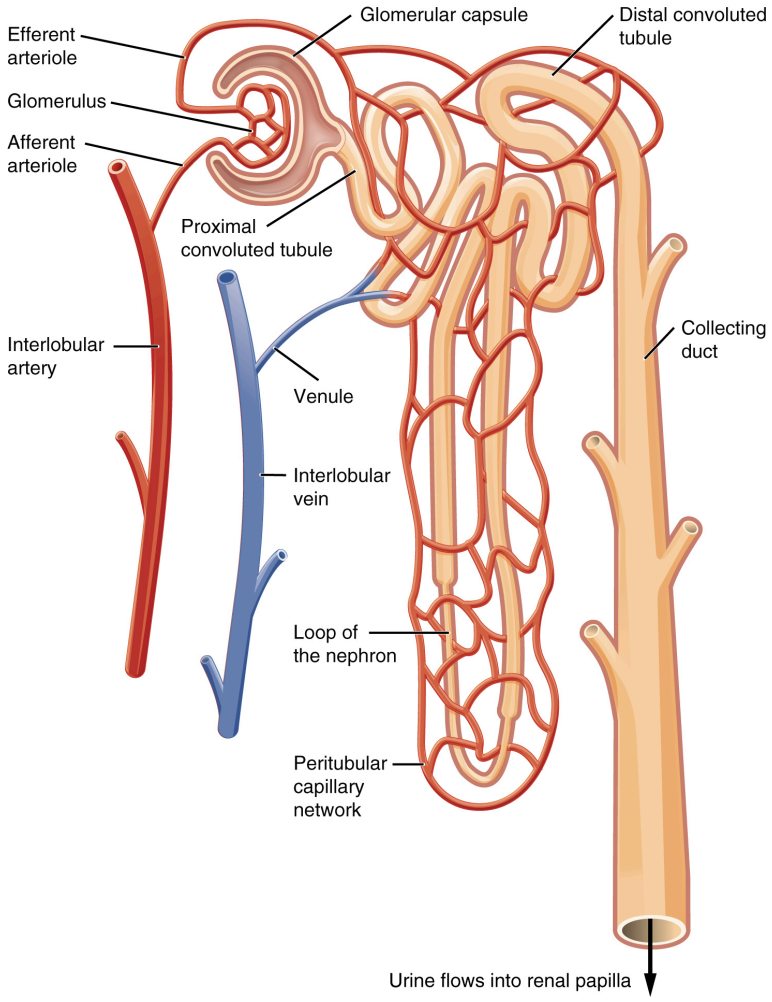


FIGURE 25.10 Blood Flow in the Nephron The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

INTERACTIVE LINK

Visit this link (http://openstax.org/l/bloodflow5) to view an interactive tutorial of the flow of blood through the kidney.

Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

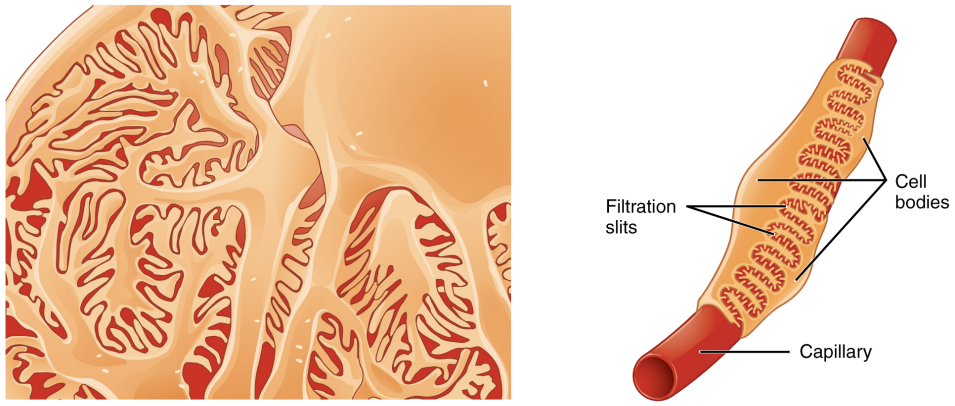


FIGURE 25.11 Podocytes Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

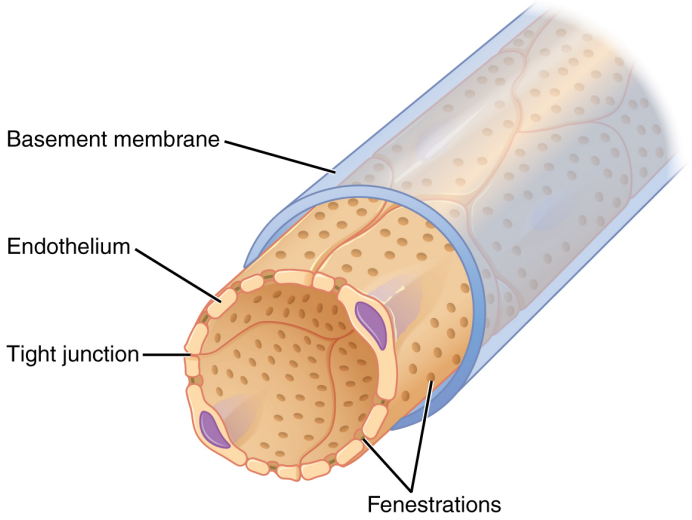


FIGURE 25.12 Fenestrated Capillary Fenestrations allow many substances to diffuse from the blood based primarily on size.

The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** (Figure 25.13). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^+ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na^+ concentration are adenosine triphosphate (ATP) and adenosine.

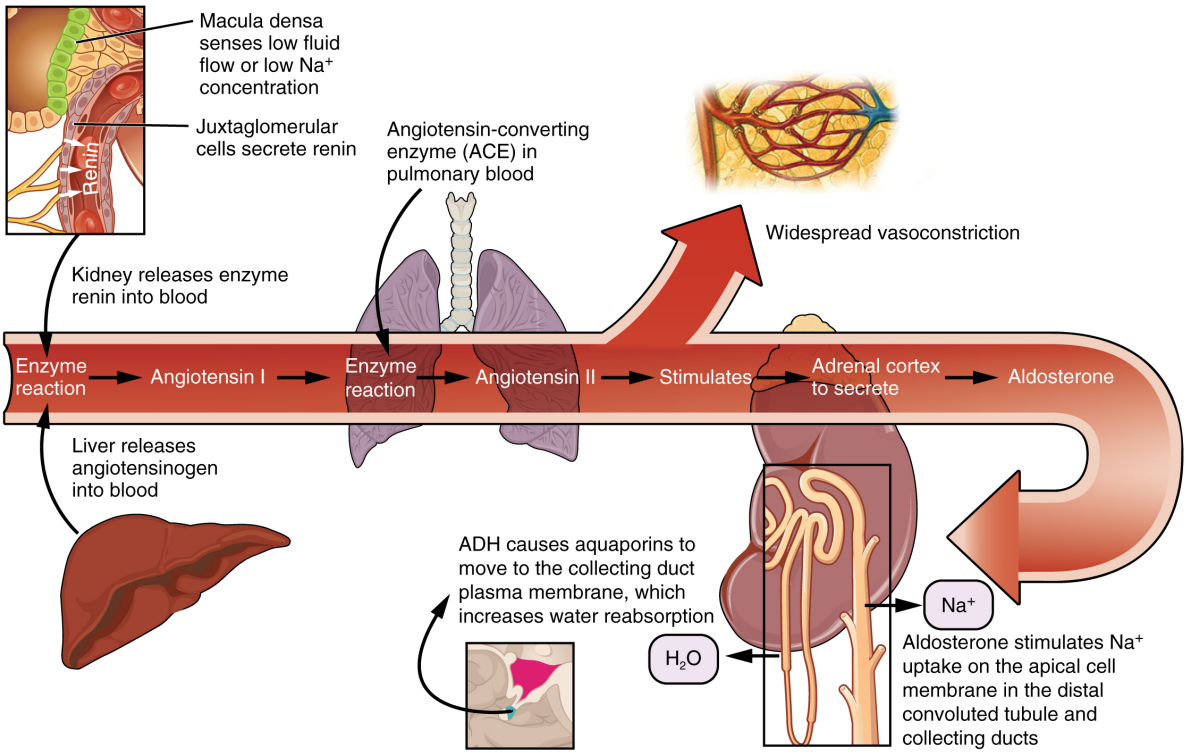


FIGURE 25.14 Conversion of Angiotensin I to Angiotensin II The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a **brush border**. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+, Cl^-, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back

Fatigue
Excessive urination
Oliguria (too little urine output)

TABLE 25.3

Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate (GFR)**. The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in males (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in females (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in males and 150 L/day in females. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day (Table 25.4).

Calculating Urine Formation per Day

	Flow per minute (mL)	Calculation
Renal blood flow	1050	Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney. 5000*0.21 = 1050 mL blood/min
Renal plasma flow	578	Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent. 1050*0.55 = 578 mL plasma/min
Glomerular filtration rate	110	The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent). 578*0.19 = 110 mL filtrate/min
Urine	1296 ml/day	The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent). 110*.008 = 0.9 mL urine /min Multiply urine/min times 60 minutes times 24 hours to get daily urine production. 0.9*60*24 = 1296 mL/day urine

TABLE 25.4

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure exceeds

NFP = GBHP – [CHP + BCOP] = 10 mm Hg

Or:

NFP = 55 – [15 + 30] = 10 mm Hg

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding 1/3 of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of **inulin**. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

25.6 Tubular Reabsorption

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts (Table 25.5 and Figure 25.17). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
HCO_3^-	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport with Cl^-; in ascending limb		Reabsorbed antiport with Cl^-
H^+	Secreted; diffusion		Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

TABLE 25.5

Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

TABLE 25.6

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term "reabsorbed." All of these substances were "absorbed" in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is "obliged" to follow the Na^+ (Figure 25.18).

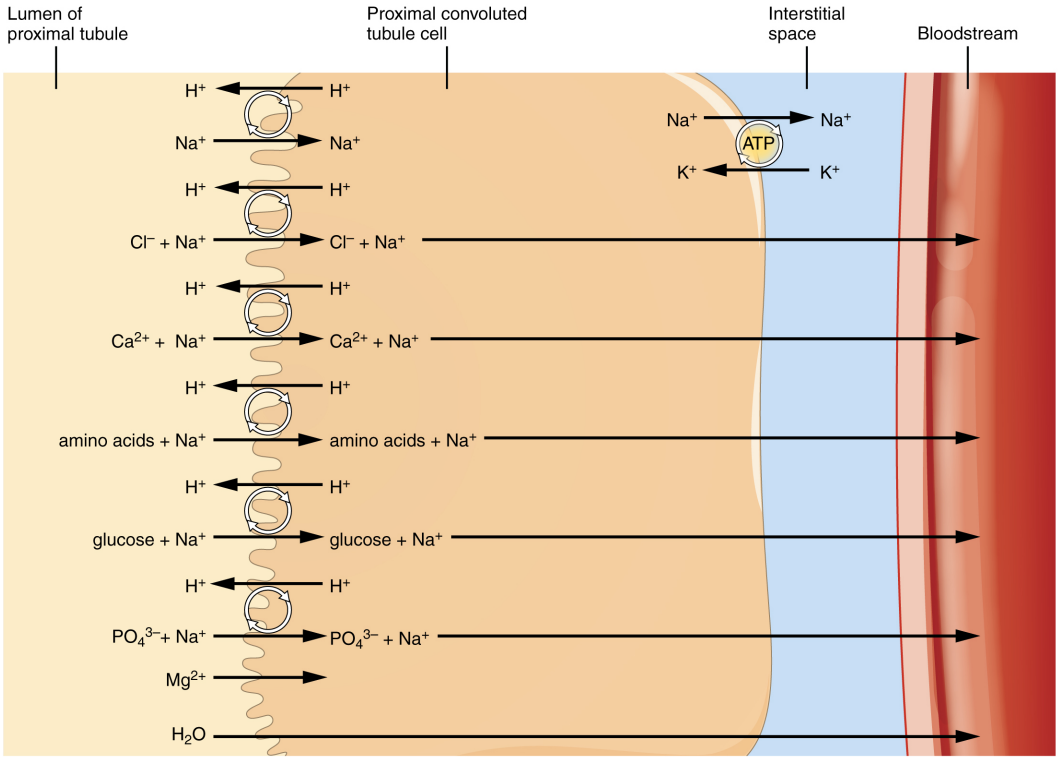


FIGURE 25.18 Substances Reabsorbed and Secreted by the PCT

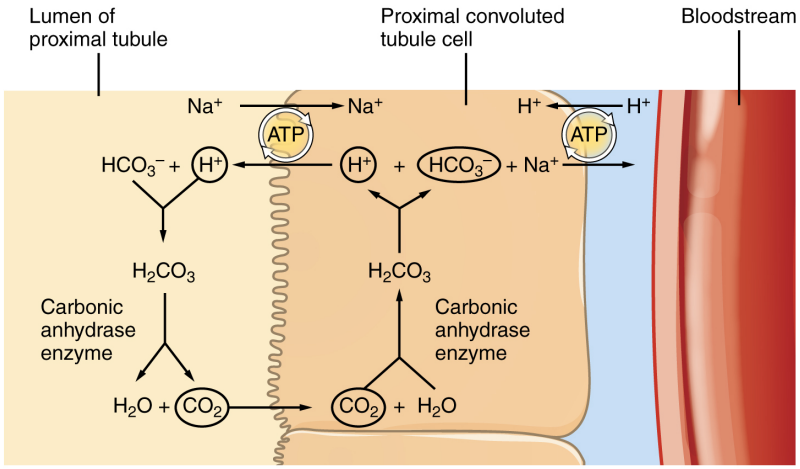


FIGURE 25.19 **Reabsorption of Bicarbonate from the PCT**

Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na^+ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg in the filtrate. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na^+, and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+ and CL^-, are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hypoosomotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The Na^+/K^+ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl^- by Na^+/Cl^- symporters in the apical membrane. At the same time that Na^+ is actively pumped from the basal side of the cell into the interstitial fluid, Cl^- follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the "back door exiting" K^+, there is one Na^+ and two Cl^- ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the

quantities of water to leave the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $Na^+/K^+/2Cl^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na^+ and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na^+ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters and is removed.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/multiplier) to learn about the countercurrent multiplier system.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na^+/K^+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na^+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl^- out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca^{++} from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca^{++} recovery from the forming urine. In addition, as Na^+ is pumped out of the cell, the resulting electrochemical gradient attracts Ca^{++} into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport Ca^{++} into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{++} not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

Arteriole Myogenic Mechanism

The **myogenic mechanism** regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

Tubuloglomerular Feedback

The **tubuloglomerular feedback** mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells (Table 25.7). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and Na^+ concentration. As GFR increases, there is less time for NaCl to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less Na^+ is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

Paracrine Mechanisms Controlling Glomerular Filtration Rate

Change in GFR	NaCl Absorption	Role of ATP and adenosine/Role of NO	Effect on GFR
Increased GFR	Tubular NaCl increases	ATP and adenosine increase, causing vasoconstriction	Vasoconstriction slows GFR
Decreased GFR	Tubular NaCl decreases	ATP and adenosine decrease, causing vasodilation	Vasodilation increases GFR
Increased GFR	Tubular NaCl increases	NO increases, causing vasodilation	Vasodilation increases GFR
Decreased GFR	Tubular NaCl decreases	NO decreases, causing vasoconstricton	Vasoconstriction decreases GFR

TABLE 25.7

people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting Na^+ recovery in the collecting ducts. If Na^+ remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both Na^+ and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a 28-amino acid peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) of 32 amino acids produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide "fine tuning" for the regulation of blood pressure. BNP's longer biologic half-life makes it a good diagnostic marker of congestive heart failure (Figure 25.21).

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands in response to decreased circulating Ca^{++} levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate (PO_3^-), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating Ca^{++} levels. By ridding the blood of phosphate, higher circulating Ca^{++} levels are permitted.

	Stimulus	Effect on GFR	Effect on RBF
VASOCONSTRICTORS			
Sympathetic nerves (epinephrine and norepinephrine)	↓ ECFV	↓	↓
Angiotensin II	↓ ECFV	↓	↓
Endothelin	↑ Stretch, bradykinin, angiotensin II, epinephrine ↓ ECFV	↓	↓
VASODILATORS			
Prostaglandins (PGE1, PGE2, and PGI2)	↓ ECFV ↑ shear stress, angiotensin II	No change/↑	↑
Nitric oxide (NO)	↑ shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine	↑	↑
Bradykinin	Prostaglandins, ↓ ACE	↑	↑
Natriuretic peptides (ANP, B-type)	↑ ECFV	↑	No change

ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF = renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide

FIGURE 25.21 Major Hormones That Influence GFR and RFB

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased thirst), and polyphagia (increased hunger).

Regulation of Extracellular Na^+

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much Na^+ present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating Na^+ concentration include the renin–angiotensin–aldosterone system and ADH (see Figure 25.14). Aldosterone stimulates the uptake of Na^+ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate Na^+ concentration indirectly by regulating the reabsorption of water.

Regulation of Extracellular K^+

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that K^+ and Na^+ concentrations will move in opposite directions. When more Na^+ is reabsorbed, more K^+ is secreted; when less Na^+ is reabsorbed (leading to excretion by the kidney), more K^+ is retained. When aldosterone causes a recovery of Na^+ in the nephron, a negative electrical gradient is created that promotes the secretion of K^+ and Cl^- into the lumen.

Regulation of Cl^-

Chloride is important in acid–base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with Na^+ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of Na^+.

Regulation of Ca^{++} and Phosphate

The parathyroid glands monitor and respond to circulating levels of Ca^{++} in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb Ca^{++} from the forming urine. When levels are adequate or high, less PTH is released and more Ca^{++} remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When Ca^{++} levels are low, PTH inhibits reabsorption of HPO_4^{2-} so that its blood level drops, allowing Ca^{++} levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more Ca^{++} from the diet.

Regulation of H^+, Bicarbonate, and pH

The acid–base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins, HCO_3^-, and ammonia have a very large capacity to absorb or release H^+ as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly (seconds to minutes) through the conversion of HCO_3^- into CO_2, which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete H^+ into the forming urine as Na^+ is reabsorbed. The body rids itself of excess H^+ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete H^+ into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate (HCO_3^-), $H_2PO_4^-$ (dihydrogen phosphate ion), or ammonia (forming NH_4^+, ammonium ion). Urine pH typically varies in a normal range from 4.5 to

absorption of Ca^{++} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{++} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{++} leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

Blood Pressure Regulation

Due to osmosis, water follows where Na^+ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na^+. ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic dieresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (see Figure 25.14). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II (Figure 25.23). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of Na^+ and its associated osmotic recovery of water. The reabsorption of Na^+ helps to raise and maintain blood pressure over a longer term.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

of solvent and solutes

leukocyte esterase enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

loop of Henle descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

macula densa cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

medulla inner region of kidney containing the renal pyramids

mesangial contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

micturition also called urination or voiding

myogenic mechanism mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady

nephrons functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

net filtration pressure (NFP) pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule

oliguria below normal urine production of 400–500 mL/day

osteomalacia softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

pedicels finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

peritubular capillaries second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

physiological sphincter sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

podocytes cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

polyuria urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

principal cell found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

proximal convoluted tubules (PCTs) tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

renal columns extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle consists of the glomerulus and Bowman's capsule

renal cortex outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

renin enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

retroperitoneal behind the peritoneum; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

sacral micturition center group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

specific gravity weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

systemic edema increased fluid retention in the interstitial spaces and cells of the body; can be seen

podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

25.5 Physiology of Urine Formation

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and colloid osmotic pressure. Under normal circumstances, hydrostatic pressure is significantly greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure, autoregulatory mechanisms, sympathetic nervous activity, and paracrine hormones. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

25.6 Tubular Reabsorption

The kidney regulates water recovery and blood pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body's fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH_3, creatinine, and some drugs are filtered or secreted as wastes. H^+ and HCO_3^- are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate (HCO_3^-) is recovered using the same enzyme, carbonic anhydrase (CA), found in erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtaglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers Na^+, reducing filtrate osmolarity to 50–100 mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase Na^+ concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates Na^+ recovery by the collecting duct.

25.7 Regulation of Renal Blood Flow

The kidneys are innervated by sympathetic nerves of the autonomic nervous system. Sympathetic nervous activity decreases blood flow to the kidney, making more blood available to other areas of the body during times of stress. The arteriolar myogenic mechanism maintains a steady blood flow by causing arteriolar smooth muscle to contract when blood pressure increases and causing it to relax when blood pressure decreases. Tubuloglomerular feedback involves paracrine signaling at the JGA to cause vasoconstriction or vasodilation to maintain a steady rate of blood flow.

25.8 Endocrine Regulation of Kidney Function

Endocrine hormones act from a distance and paracrine hormones act locally. The renal enzyme renin converts angiotensinogen into angiotensin I. The lung enzyme, ACE, converts angiotensin I into active angiotensin II.

6. Which part of the urinary system is *not* completely retroperitoneal?
   a. kidneys
   b. ureters
   c. bladder
   d. nephrons

7. The renal pyramids are separated from each other by extensions of the renal cortex called _____.
   a. renal medulla
   b. minor calyces
   c. medullary cortices
   d. renal columns

8. The primary structure found within the medulla is the _____.
   a. loop of Henle
   b. minor calyces
   c. portal system
   d. ureter

9. The right kidney is slightly lower because _____.
   a. it is displaced by the liver
   b. it is displace by the heart
   c. it is slightly smaller
   d. it needs protection of the lower ribs

10. Blood filtrate is captured in the lumen of the _____.
   a. glomerulus
   b. Bowman's capsule
   c. calyces
   d. renal papillae

11. What are the names of the capillaries following the efferent arteriole?
   a. arcuate and medullary
   b. interlobar and interlobular
   c. peritubular and vasa recta
   d. peritubular and medullary

12. The functional unit of the kidney is called _____.
   a. the renal hilus
   b. the renal corpuscle
   c. the nephron
   d. Bowman's capsule

13. _____ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.
   a. Osmotic
   b. Hydrostatic

14. Production of urine to modify plasma makeup is the result of _____.
   a. filtration
   b. absorption
   c. secretion
   d. filtration, absorption, and secretion

15. Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs.
   a. true
   b. false

16. Aquaporin channels are only found in the collecting duct.
   a. true
   b. false

17. Most absorption and secretion occurs in this part of the nephron.
   a. proximal convoluted tubule
   b. descending loop of Henle
   c. ascending loop of Henle
   d. distal convoluted tubule
   e. collecting ducts

18. The fine tuning of water recovery or disposal occurs in _____.
   a. the proximal convoluted tubule
   b. the collecting ducts
   c. the ascending loop of Henle
   d. the distal convoluted tubule

19. Vasodilation of blood vessels to the kidneys is due to _____.
   a. more frequent action potentials
   b. less frequent action potentials

20. When blood pressure increases, blood vessels supplying the kidney will _____ to mount a steady rate of filtration.
   a. contract
   b. relax

21. Which of these three paracrine chemicals cause vasodilation?
   a. ATP
   b. adenosine
   c. nitric oxide

22. What hormone directly opposes the actions of natriuretic hormones?
   a. renin
   b. nitric oxide
   c. dopamine
   d. aldosterone

The chemical reactions of life take place in aqueous solutions. The dissolved substances in a solution are called solutes. In the human body, solutes vary in different parts of the body, but may include proteins—including those that transport lipids, carbohydrates, and, very importantly, electrolytes. Often in medicine, a mineral dissociated from a salt that carries an electrical charge (an ion) is called an electrolyte. For instance, sodium ions (Na^+) and chloride ions (Cl^-) are often referred to as electrolytes.

In the body, water moves through semi-permeable membranes of cells and from one compartment of the body to another by a process called osmosis. Osmosis is basically the diffusion of water from regions of higher concentration of water to regions of lower concentration of water, along an osmotic gradient across a semi-permeable membrane. As a result, water will move into and out of cells and tissues, depending on the relative concentrations of the water and solutes found there. An appropriate balance of solutes inside and outside of cells must be maintained to ensure normal function.

Body Water Content

Human beings are mostly water, ranging from about 75 percent of body mass in infants to about 50–60 percent in adults, to as low as 45 percent in old age. The percent of body water changes with development, because the proportions of the body given over to each organ and to muscles, fat, bone, and other tissues change from infancy to adulthood (Figure 26.2). Your brain and kidneys have the highest proportions of water, which composes 80–85 percent of their masses. In contrast, teeth have the lowest proportion of water, at 8–10 percent.

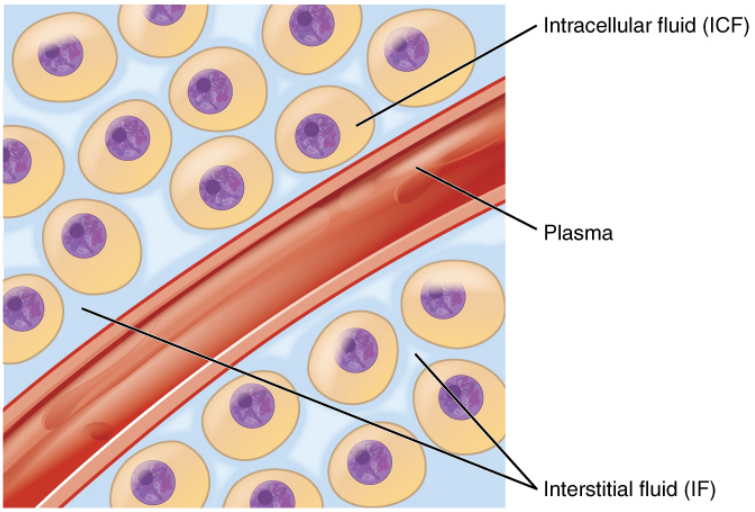


FIGURE 26.3 Fluid Compartments in the Human Body The intracellular fluid (ICF) is the fluid within cells. The interstitial fluid (IF) is part of the extracellular fluid (ECF) between the cells. Blood plasma is the second part of the ECF. Materials travel between cells and the plasma in capillaries through the IF.

Intracellular Fluid

The ICF lies within cells and is the principal component of the cytosol/cytoplasm. The ICF makes up about 60 percent of the total water in the human body, and in an average-size adult male, the ICF accounts for about 25 liters (seven gallons) of fluid (Figure 26.4). This fluid volume tends to be very stable, because the amount of water in living cells is closely regulated. If the amount of water inside a cell falls to a value that is too low, the cytosol becomes too concentrated with solutes to carry on normal cellular activities; if too much water enters a cell, the cell may burst and be destroyed.

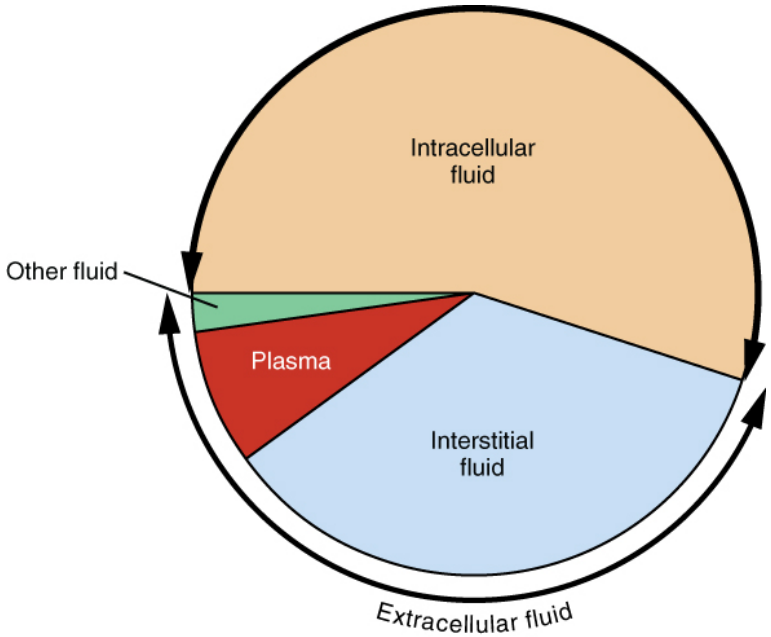


FIGURE 26.4 A Pie Graph Showing the Proportion of Total Body Fluid in Each of the Body's Fluid Compartments Most of the water in the body is intracellular fluid. The second largest volume is the interstitial fluid, which surrounds cells that are not blood cells.

Extracellular Fluid

The ECF accounts for the other one-third of the body's water content. Approximately 20 percent of the ECF is found in plasma. Plasma travels through the body in blood vessels and transports a range of materials, including blood cells, proteins (including clotting factors and antibodies), electrolytes, nutrients, gases, and wastes. Gases, nutrients, and waste materials travel between capillaries and cells through the IF. Cells are separated from the IF by a selectively permeable cell membrane that helps regulate the passage of materials between the IF and the interior

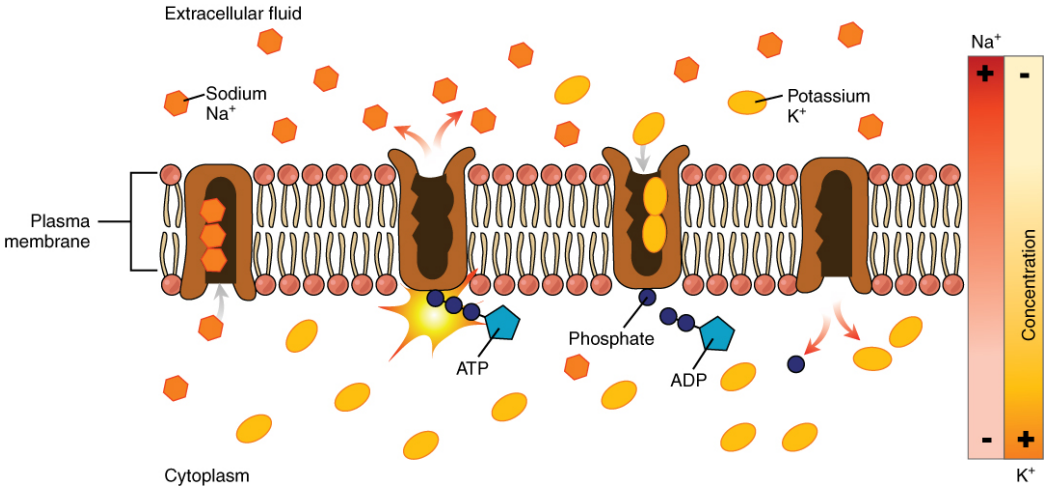


FIGURE 26.6 The Sodium-Potassium Pump The sodium-potassium pump is powered by ATP to transfer sodium out of the cytoplasm and into the ECF. The pump also transfers potassium out of the ECF and into the cytoplasm. (credit: modification of work by Mariana Ruiz Villarreal)

Fluid Movement between Compartments

Hydrostatic pressure, the force exerted by a fluid against a wall, causes movement of fluid between compartments. The hydrostatic pressure of blood is the pressure exerted by blood against the walls of the blood vessels by the pumping action of the heart. In capillaries, hydrostatic pressure (also known as capillary blood pressure) is higher than the opposing "colloid osmotic pressure" in blood—a "constant" pressure primarily produced by circulating albumin—at the arteriolar end of the capillary (Figure 26.7). This pressure forces plasma and nutrients out of the capillaries and into surrounding tissues. Fluid and the cellular wastes in the tissues enter the capillaries at the venule end, where the hydrostatic pressure is less than the osmotic pressure in the vessel. Filtration pressure squeezes fluid from the plasma in the blood to the IF surrounding the tissue cells. The surplus fluid in the interstitial space that is not returned directly back to the capillaries is drained from tissues by the lymphatic system, and then re-enters the vascular system at the subclavian veins.

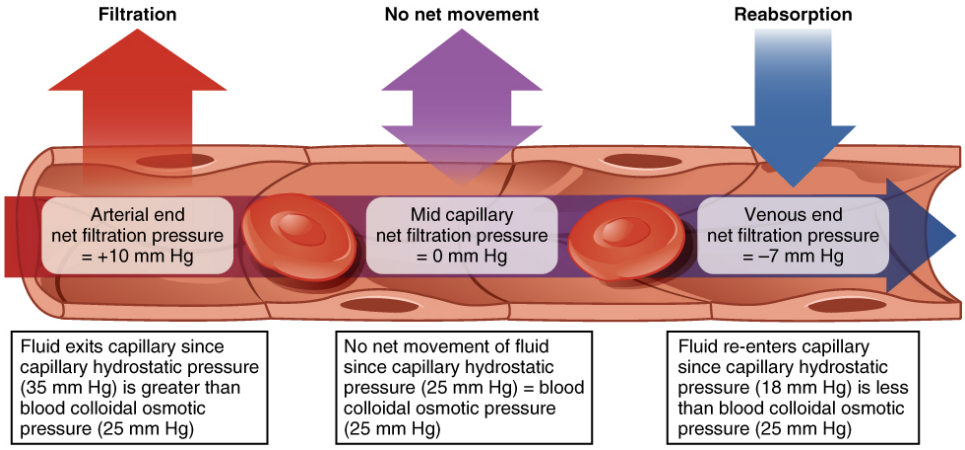


FIGURE 26.7 Capillary Exchange Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint of the capillary since CHP = BCOP. Net reabsorption occurs near the venous end of the capillary since BCOP is greater than CHP.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/dynamicfluid) to see an explanation of the dynamics of fluid in the body's compartments. What happens in the tissue when capillary blood pressure is less than osmotic pressure?

Hydrostatic pressure is especially important in governing the movement of water in the nephrons of the kidneys to ensure proper filtering of the blood to form urine. As hydrostatic pressure in the kidneys increases, the amount of water leaving the capillaries also increases, and more urine filtrate is formed. If hydrostatic pressure in the kidneys

Disorders of the...

Fluid Balance: Edema

Edema is the accumulation of excess water in the tissues. It is most common in the soft tissues of the extremities. The physiological causes of edema include water leakage from blood capillaries. Edema is almost always caused by an underlying medical condition, by the use of certain therapeutic drugs, by pregnancy, by localized injury, or by an allergic reaction. In the limbs, the symptoms of edema include swelling of the subcutaneous tissues, an increase in the normal size of the limb, and stretched, tight skin. One quick way to check for subcutaneous edema localized in a limb is to press a finger into the suspected area. Edema is likely if the depression persists for several seconds after the finger is removed (which is called "pitting").

Pulmonary edema is excess fluid in the air sacs of the lungs, a common symptom of heart and/or kidney failure. People with pulmonary edema likely will experience difficulty breathing, and they may experience chest pain. Pulmonary edema can be life threatening, because it compromises gas exchange in the lungs, and anyone having symptoms should immediately seek medical care.

In pulmonary edema resulting from heart failure, excessive leakage of water occurs because fluids get "backed up" in the pulmonary capillaries of the lungs, when the left ventricle of the heart is unable to pump sufficient blood into the systemic circulation. Because the left side of the heart is unable to pump out its normal volume of blood, the blood in the pulmonary circulation gets "backed up," starting with the left atrium, then into the pulmonary veins, and then into pulmonary capillaries. The resulting increased hydrostatic pressure within pulmonary capillaries, as blood is still coming in from the pulmonary arteries, causes fluid to be pushed out of them and into lung tissues.

Other causes of edema include damage to blood vessels and/or lymphatic vessels, or a decrease in osmotic pressure in chronic and severe liver disease, where the liver is unable to manufacture plasma proteins (Figure 26.9). A decrease in the normal levels of plasma proteins results in a decrease of colloid osmotic pressure (which counterbalances the hydrostatic pressure) in the capillaries. This process causes loss of water from the blood to the surrounding tissues, resulting in edema.



FIGURE 26.9 Edema An allergic reaction can cause capillaries in the hand to leak excess fluid that accumulates in the tissues. (credit: Jane Whitney)

Mild, transient edema of the feet and legs may be caused by sitting or standing in the same position for long periods of time, as in the work of a toll collector or a supermarket cashier. This is because deep veins in the lower limbs rely on skeletal muscle contractions to push on the veins and thus "pump" blood back to the heart. Otherwise, the venous blood pools in the lower limbs and can leak into surrounding tissues.

Medications that can result in edema include vasodilators, calcium channel blockers used to treat hypertension,

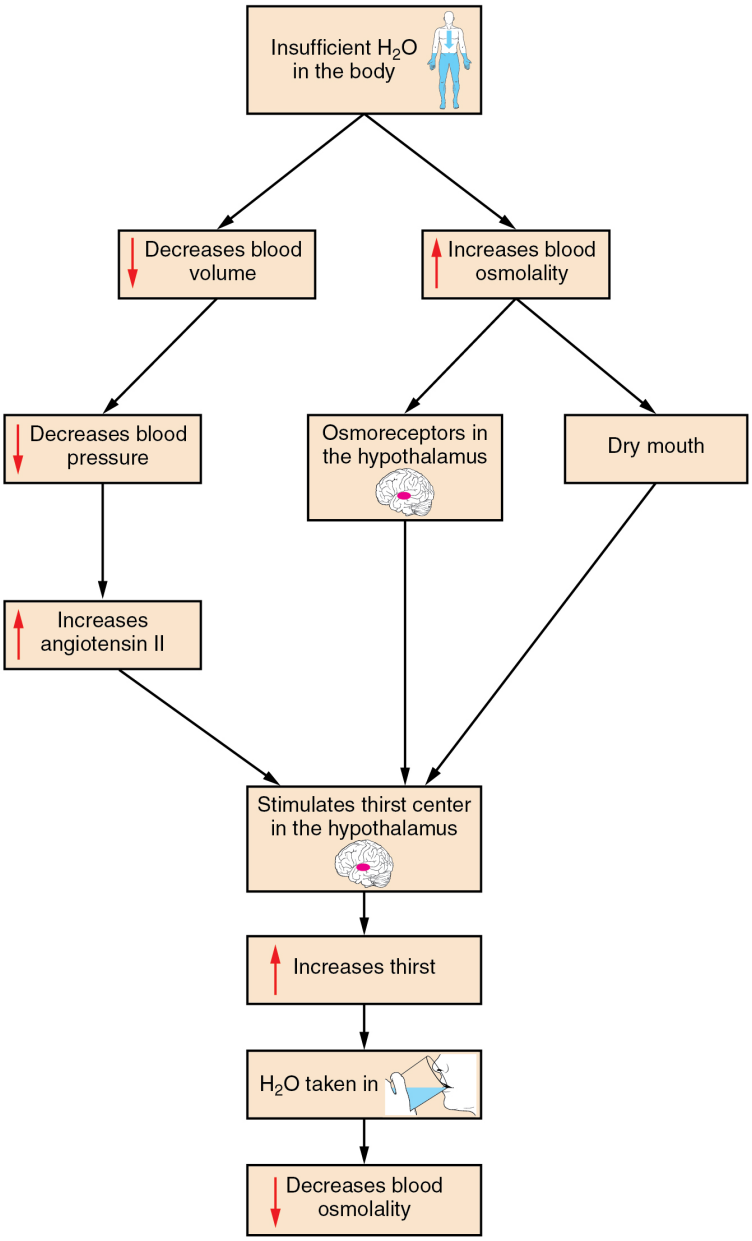


FIGURE 26.10 A Flowchart Showing the Thirst Response The thirst response begins when osmoreceptors detect a decrease in water levels in the blood.

Decreased blood volume resulting from water loss has two additional effects. First, baroreceptors, blood-pressure receptors in the arch of the aorta and the carotid arteries in the neck, detect a decrease in blood pressure that results from decreased blood volume. The heart is ultimately signaled to increase its rate and/or strength of contractions to compensate for the lowered blood pressure.

Second, the kidneys have a renin-angiotensin hormonal system that increases the production of the active form of the hormone angiotensin II, which helps stimulate thirst, but also stimulates the release of the hormone aldosterone from the adrenal glands. Aldosterone increases the reabsorption of sodium in the distal tubules of the nephrons in the kidneys, and water follows this reabsorbed sodium back into the blood.

If adequate fluids are not consumed, dehydration results and a person's body contains too little water to function correctly. A person who repeatedly vomits or who has diarrhea may become dehydrated, and infants, because their body mass is so low, can become dangerously dehydrated very quickly. Endurance athletes such as distance runners often become dehydrated during long races. Dehydration can be a medical emergency, and a dehydrated person may lose consciousness, become comatose, or die, if their body is not rehydrated quickly.

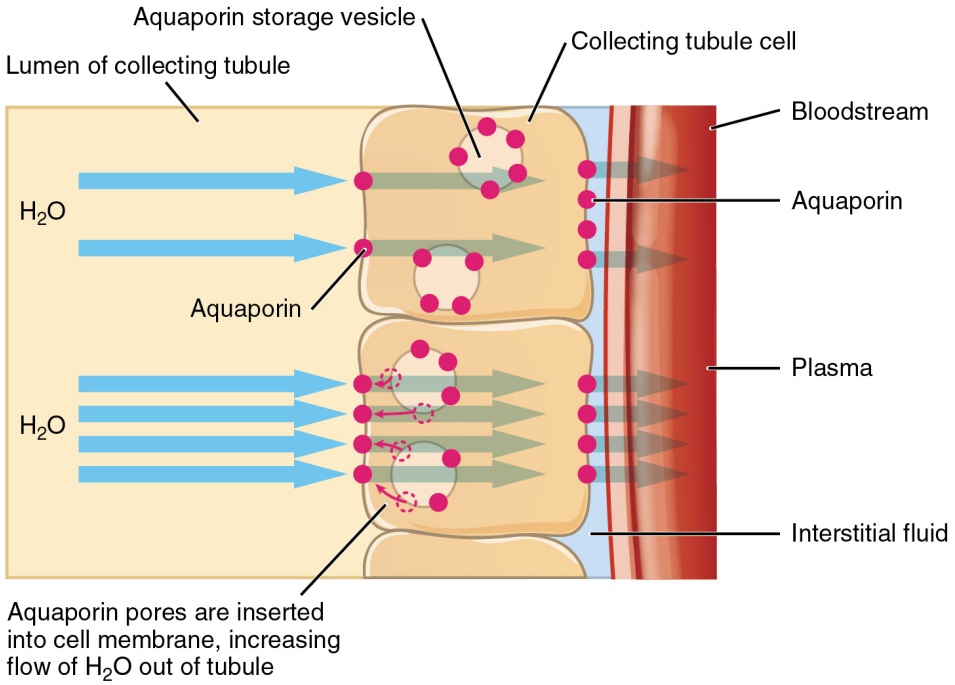


FIGURE 26.12 Aquaporins The binding of ADH to receptors on the cells of the collecting tubule results in aquaporins being inserted into the plasma membrane, shown in the lower cell. This dramatically increases the flow of water out of the tubule and into the bloodstream.

A diuretic is a compound that increases urine output and therefore decreases water conservation by the body. Diuretics are used to treat hypertension, congestive heart failure, and fluid retention associated with menstruation. Alcohol acts as a diuretic by inhibiting the release of ADH. Additionally, caffeine, when consumed in high concentrations, acts as a diuretic.

26.3 Electrolyte Balance

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- List the role of the six most important electrolytes in the body
- Name the disorders associated with abnormally high and low levels of the six electrolytes
- Identify the predominant extracellular anion
- Describe the role of aldosterone on the level of water in the body

The body contains a large variety of ions, or electrolytes, which perform a variety of functions. Some ions assist in the transmission of electrical impulses along cell membranes in neurons and muscles. Other ions help to stabilize protein structures in enzymes. Still others aid in releasing hormones from endocrine glands. All of the ions in plasma contribute to the osmotic balance that controls the movement of water between cells and their environment.

Electrolytes in living systems include sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, copper, zinc, iron, manganese, molybdenum, copper, and chromium. In terms of body functioning, six electrolytes are most important: sodium, potassium, chloride, bicarbonate, calcium, and phosphate.

Roles of Electrolytes

These six ions aid in nerve excitability, endocrine secretion, membrane permeability, buffering body fluids, and controlling the movement of fluids between compartments. These ions enter the body through the digestive tract. More than 90 percent of the calcium and phosphate that enters the body is incorporated into bones and teeth, with bone serving as a mineral reserve for these ions. In the event that calcium and phosphate are needed for other functions, bone tissue can be broken down to supply the blood and other tissues with these minerals. Phosphate is a normal constituent of nucleic acids; hence, blood levels of phosphate will increase whenever nucleic acids are broken down.

result in higher-than-normal sodium values.

Potassium

Potassium is the major intracellular cation. It helps establish the resting membrane potential in neurons and muscle fibers after membrane depolarization and action potentials. In contrast to sodium, potassium has very little effect on osmotic pressure. The low levels of potassium in blood and CSF are due to the sodium-potassium pumps in cell membranes, which maintain the normal potassium concentration gradients between the ICF and ECF. The recommendation for daily intake/consumption of potassium is 4700 mg. Potassium is excreted, both actively and passively, through the renal tubules, especially the distal convoluted tubule and collecting ducts. Potassium participates in the exchange with sodium in the renal tubules under the influence of aldosterone, which also relies on basolateral sodium-potassium pumps.

Hypokalemia is an abnormally low potassium blood level. Similar to the situation with hyponatremia, hypokalemia can occur because of either an absolute reduction of potassium in the body or a relative reduction of potassium in the blood due to the redistribution of potassium. An absolute loss of potassium can arise from decreased intake, frequently related to starvation. It can also come about from vomiting, diarrhea, or alkalosis.

Some insulin-dependent diabetic patients experience a relative reduction of potassium in the blood from the redistribution of potassium. When insulin is administered and glucose is taken up by cells, potassium passes through the cell membrane along with glucose, decreasing the amount of potassium in the blood and IF, which can cause hyperpolarization of the cell membranes of neurons, reducing their responses to stimuli.

Hyperkalemia, an elevated potassium blood level, also can impair the function of skeletal muscles, the nervous system, and the heart. Hyperkalemia can result from increased dietary intake of potassium. In such a situation, potassium from the blood ends up in the ECF in abnormally high concentrations. This can result in a partial depolarization (excitation) of the plasma membrane of skeletal muscle fibers, neurons, and cardiac cells of the heart, and can also lead to an inability of cells to repolarize. For the heart, this means that it won't relax after a contraction, and will effectively "seize" and stop pumping blood, which is fatal within minutes. Because of such effects on the nervous system, a person with hyperkalemia may also exhibit mental confusion, numbness, and weakened respiratory muscles.

Chloride

Chloride is the predominant extracellular anion. Chloride is a major contributor to the osmotic pressure gradient between the ICF and ECF, and plays an important role in maintaining proper hydration. Chloride functions to balance cations in the ECF, maintaining the electrical neutrality of this fluid. The paths of secretion and reabsorption of chloride ions in the renal system follow the paths of sodium ions.

Hypochloremia, or lower-than-normal blood chloride levels, can occur because of defective renal tubular absorption. Vomiting, diarrhea, and metabolic acidosis can also lead to hypochloremia. **Hyperchloremia**, or higher-than-normal blood chloride levels, can occur due to dehydration, excessive intake of dietary salt (NaCl) or swallowing of sea water, aspirin intoxication, congestive heart failure, and the hereditary, chronic lung disease, cystic fibrosis. In people who have cystic fibrosis, chloride levels in sweat are two to five times those of normal levels, and analysis of sweat is often used in the diagnosis of the disease.

INTERACTIVE LINK

Read this article (http://openstax.org/l/saltwater) for an explanation of the effect of seawater on humans. What effect does drinking seawater have on the body?

Bicarbonate

Bicarbonate is the second most abundant anion in the blood. Its principal function is to maintain your body's acid-base balance by being part of buffer systems. This role will be discussed in a different section.

Bicarbonate ions result from a chemical reaction that starts with carbon dioxide (CO_2) and water, two molecules that are produced at the end of aerobic metabolism. Only a small amount of CO_2 can be dissolved in body fluids. Thus, over 90 percent of the CO_2 is converted into bicarbonate ions, HCO_3^-, through the following reactions:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

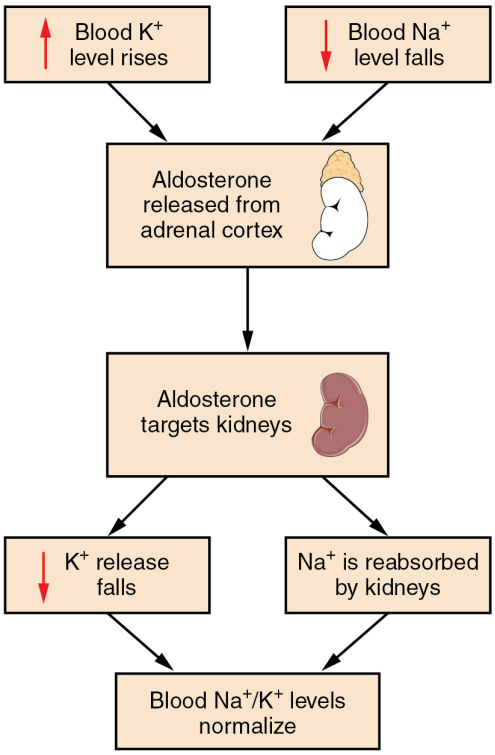


FIGURE 26.13 The Aldosterone Feedback Loop Aldosterone, which is released by the adrenal gland, facilitates reabsorption of Na^+ and thus the reabsorption of water.

Angiotensin II

Angiotensin II causes vasoconstriction and an increase in systemic blood pressure. This action increases the glomerular filtration rate, resulting in more material filtered out of the glomerular capillaries and into Bowman's capsule. Angiotensin II also signals an increase in the release of aldosterone from the adrenal cortex.

In the distal convoluted tubules and collecting ducts of the kidneys, aldosterone stimulates the synthesis and activation of the sodium-potassium pump (Figure 26.14). Sodium passes from the filtrate, into and through the cells of the tubules and ducts, into the ECF and then into capillaries. Water follows the sodium due to osmosis. Thus, aldosterone causes an increase in blood sodium levels and blood volume. Aldosterone's effect on potassium is the reverse of that of sodium; under its influence, excess potassium is pumped into the renal filtrate for excretion from the body.

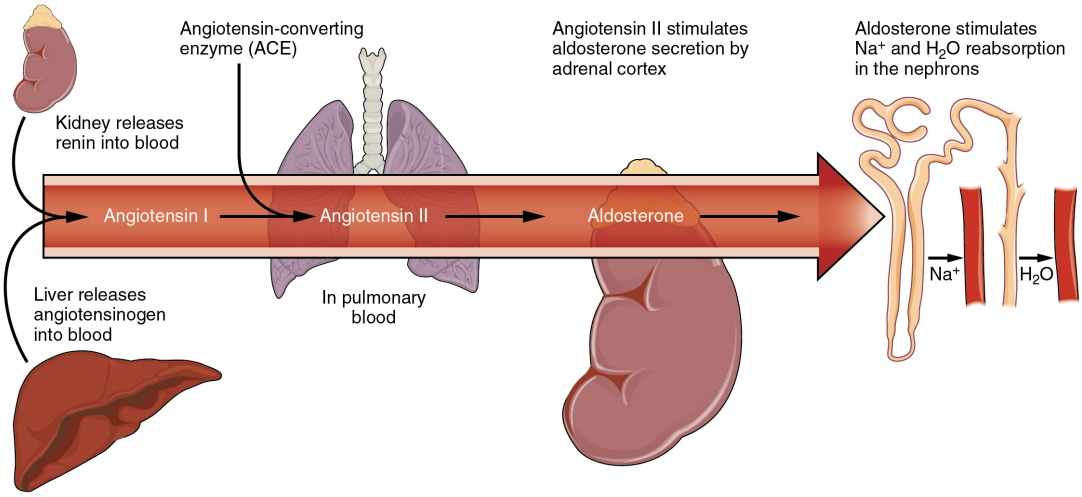


FIGURE 26.14 The Renin-Angiotensin System Angiotensin II stimulates the release of aldosterone from the adrenal cortex.

pH	Examples of solutions
0	Battery acid, strong hydrofluoric acid
1	Hydrochloric acid secreted by stomach lining
2	Lemon juice, gastric acid, vinegar
3	Grapefruit juice, orange juice, soda
4	Tomato juice, acid rain
5	Soft drinking water, black coffee
6	Urine, saliva
7	“Pure” water
8	Sea water
9	Baking soda
10	Great Salt Lake, milk of magnesia
11	Ammonia solution
12	Soapy water
13	Bleach, oven cleaner
14	Liquid drain cleaner

FIGURE 26.15 The pH Scale This chart shows where many common substances fall on the pH scale.

Buffer Systems in the Body

The buffer systems in the human body are extremely efficient, and different systems work at different rates. It takes only seconds for the chemical buffers in the blood to make adjustments to pH. The respiratory tract can adjust the blood pH upward in minutes by exhaling CO_2 from the body. The renal system can also adjust blood pH through the excretion of hydrogen ions (H^+) and the conservation of bicarbonate, but this process takes hours to days to have an effect.

The buffer systems functioning in blood plasma include plasma proteins, phosphate, and bicarbonate and carbonic acid buffers. The kidneys help control acid-base balance by excreting hydrogen ions and generating bicarbonate that helps maintain blood plasma pH within a normal range. Protein buffer systems work predominantly inside cells.

Protein Buffers in Blood Plasma and Cells

Nearly all proteins can function as buffers. Proteins are made up of amino acids, which contain positively charged amino groups and negatively charged carboxyl groups. The charged regions of these molecules can bind hydrogen and hydroxyl ions, and thus function as buffers. Buffering by proteins accounts for two-thirds of the buffering power of the blood and most of the buffering within cells.

Hemoglobin as a Buffer

Hemoglobin is the principal protein inside of red blood cells and accounts for one-third of the mass of the cell. During the conversion of CO_2 into bicarbonate, hydrogen ions liberated in the reaction are buffered by hemoglobin,

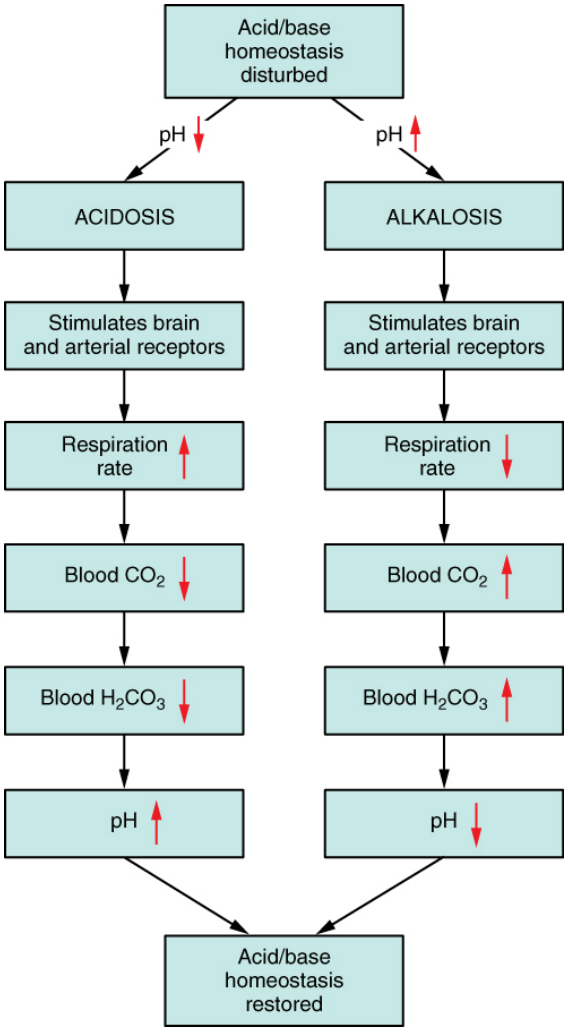


FIGURE 26.16 Respiratory Regulation of Blood pH The respiratory system can reduce blood pH by removing CO_2 from the blood.

The chemical reactions that regulate the levels of CO_2 and carbonic acid occur in the lungs when blood travels through the lung's pulmonary capillaries. Minor adjustments in breathing are usually sufficient to adjust the pH of the blood by changing how much CO_2 is exhaled. In fact, doubling the respiratory rate for less than 1 minute, removing "extra" CO_2, would increase the blood pH by 0.2. This situation is common if you are exercising strenuously over a period of time. To keep up the necessary energy production, you would produce excess CO_2 (and lactic acid if exercising beyond your aerobic threshold). In order to balance the increased acid production, the respiration rate goes up to remove the CO_2. This helps to keep you from developing acidosis.

The body regulates the respiratory rate by the use of chemoreceptors, which primarily use CO_2 as a signal. Peripheral blood sensors are found in the walls of the aorta and carotid arteries. These sensors signal the brain to provide immediate adjustments to the respiratory rate if CO_2 levels rise or fall. Yet other sensors are found in the brain itself. Changes in the pH of CSF affect the respiratory center in the medulla oblongata, which can directly modulate breathing rate to bring the pH back into the normal range.

Hypercapnia, or abnormally elevated blood levels of CO_2, occurs in any situation that impairs respiratory functions, including pneumonia and congestive heart failure. Reduced breathing (hypoventilation) due to drugs such as morphine, barbiturates, or ethanol (or even just holding one's breath) can also result in hypercapnia. **Hypocapnia**, or abnormally low blood levels of CO_2, occurs with any cause of hyperventilation that drives off the CO_2, such as salicylate toxicity, elevated room temperatures, fever, or hysteria.

Renal Regulation of Acid-Base Balance

The renal regulation of the body's acid-base balance addresses the metabolic component of the buffering system.

bicarbonate by the renal system.

Disorders of the...

Acid-Base Balance: Ketoacidosis

Diabetic acidosis, or ketoacidosis, occurs most frequently in people with poorly controlled diabetes mellitus. When certain tissues in the body cannot get adequate amounts of glucose, they depend on the breakdown of fatty acids for energy. When acetyl groups break off the fatty acid chains, the acetyl groups then non-enzymatically combine to form ketone bodies, acetoacetic acid, beta-hydroxybutyric acid, and acetone, all of which increase the acidity of the blood. In this condition, the brain isn't supplied with enough of its fuel—glucose—to produce all of the ATP it requires to function.

Ketoacidosis can be severe and, if not detected and treated properly, can lead to diabetic coma, which can be fatal. A common early symptom of ketoacidosis is deep, rapid breathing as the body attempts to drive off CO_2 and compensate for the acidosis. Another common symptom is fruity-smelling breath, due to the exhalation of acetone. Other symptoms include dry skin and mouth, a flushed face, nausea, vomiting, and stomach pain. Treatment for diabetic coma is ingestion or injection of sugar; its prevention is the proper daily administration of insulin.

A person who is diabetic and uses insulin can initiate ketoacidosis if a dose of insulin is missed. Among people with type 2 diabetes, those of Hispanic and African-American descent are more likely to go into ketoacidosis than those of other ethnic backgrounds, although the reason for this is unknown.

26.5 Disorders of Acid-Base Balance

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Identify the three blood variables considered when making a diagnosis of acidosis or alkalosis
- Identify the source of compensation for blood pH problems of a respiratory origin
- Identify the source of compensation for blood pH problems of a metabolic/renal origin

Normal arterial blood pH is restricted to a very narrow range of 7.35 to 7.45. A person who has a blood pH below 7.35 is considered to be in acidosis (actually, "physiological acidosis," because blood is not truly acidic until its pH drops below 7), and a continuous blood pH below 7.0 can be fatal. Acidosis has several symptoms, including headache and confusion, and the individual can become lethargic and easily fatigued (Figure 26.18). A person who has a blood pH above 7.45 is considered to be in alkalosis, and a pH above 7.8 is fatal. Some symptoms of alkalosis include cognitive impairment (which can progress to unconsciousness), tingling or numbness in the extremities, muscle twitching and spasm, and nausea and vomiting. Both acidosis and alkalosis can be caused by either metabolic or respiratory disorders.

As discussed earlier in this chapter, the concentration of carbonic acid in the blood is dependent on the level of CO_2 in the body and the amount of CO_2 gas exhaled through the lungs. Thus, the respiratory contribution to acid-base balance is usually discussed in terms of CO_2 (rather than of carbonic acid). Remember that a molecule of carbonic acid is lost for every molecule of CO_2 exhaled, and a molecule of carbonic acid is formed for every molecule of CO_2 retained.

Strenuous exercise can cause temporary metabolic acidosis due to the production of lactic acid. The last five causes result from the ingestion of specific substances. The active form of aspirin is its metabolite, sulfasalicylic acid. An overdose of aspirin causes acidosis due to the acidity of this metabolite. Metabolic acidosis can also result from uremia, which is the retention of urea and uric acid. Metabolic acidosis can also arise from diabetic ketoacidosis, wherein an excess of ketone bodies are present in the blood. Other causes of metabolic acidosis are a decrease in the excretion of hydrogen ions, which inhibits the conservation of bicarbonate ions, and excessive loss of bicarbonate ions through the gastrointestinal tract due to diarrhea.

Metabolic Alkalosis: Primary Bicarbonate Excess

Metabolic alkalosis is the opposite of metabolic acidosis. It occurs when the blood is too alkaline (pH above 7.45) due to too much bicarbonate (called primary bicarbonate excess).

A transient excess of bicarbonate in the blood can follow ingestion of excessive amounts of bicarbonate, citrate, or antacids for conditions such as stomach acid reflux—known as heartburn. Cushing's disease, which is the chronic hypersecretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, can cause chronic metabolic alkalosis. The oversecretion of ACTH results in elevated aldosterone levels and an increased loss of potassium by urinary excretion. Other causes of metabolic alkalosis include the loss of hydrochloric acid from the stomach through vomiting, potassium depletion due to the use of diuretics for hypertension, and the excessive use of laxatives.

Respiratory Acidosis: Primary Carbonic Acid/CO_2 Excess

Respiratory acidosis occurs when the blood is overly acidic due to an excess of carbonic acid, resulting from too much CO_2 in the blood. Respiratory acidosis can result from anything that interferes with respiration, such as pneumonia, emphysema, or congestive heart failure.

Respiratory Alkalosis: Primary Carbonic Acid/CO_2 Deficiency

Respiratory alkalosis occurs when the blood is overly alkaline due to a deficiency in carbonic acid and CO_2 levels in the blood. This condition usually occurs when too much CO_2 is exhaled from the lungs, as occurs in hyperventilation, which is breathing that is deeper or more frequent than normal. An elevated respiratory rate leading to hyperventilation can be due to extreme emotional upset or fear, fever, infections, hypoxia, or abnormally high levels of catecholamines, such as epinephrine and norepinephrine. Surprisingly, aspirin overdose—salicylate toxicity—can result in respiratory alkalosis as the body tries to compensate for initial acidosis.

INTERACTIVE LINK

Watch this video (http://openstax.org/l/altitude) to see a demonstration of the effect altitude has on blood pH. What effect does high altitude have on blood pH, and why?

Compensation Mechanisms

Various compensatory mechanisms exist to maintain blood pH within a narrow range, including buffers, respiration, and renal mechanisms. Although compensatory mechanisms usually work very well, when one of these mechanisms is not working properly (like kidney failure or respiratory disease), they have their limits. If the pH and bicarbonate to carbonic acid ratio are changed too drastically, the body may not be able to compensate. Moreover, extreme changes in pH can denature proteins. Extensive damage to proteins in this way can result in disruption of normal metabolic processes, serious tissue damage, and ultimately death.

Respiratory Compensation

Respiratory compensation for metabolic acidosis increases the respiratory rate to drive off CO_2 and readjust the bicarbonate to carbonic acid ratio to the 20:1 level. This adjustment can occur within minutes. Respiratory compensation for metabolic alkalosis is not as adept as its compensation for acidosis. The normal response of the respiratory system to elevated pH is to increase the amount of CO_2 in the blood by decreasing the respiratory rate to conserve CO_2. There is a limit to the decrease in respiration, however, that the body can tolerate. Hence, the respiratory route is less efficient at compensating for metabolic alkalosis than for acidosis.

Key Terms

antidiuretic hormone (ADH) also known as vasopressin, a hormone that increases the volume of water reabsorbed from the collecting tubules of the kidney

dehydration state of containing insufficient water in blood and other tissues

dihydroxyvitamin D active form of vitamin D required by the intestinal epithelial cells for the absorption of calcium

diuresis excess production of urine

extracellular fluid (ECF) fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluids found in other reservoirs in the body

fluid compartment fluid inside all cells of the body constitutes a compartment system that is largely segregated from other systems

hydrostatic pressure pressure exerted by a fluid against a wall, caused by its own weight or pumping force

hypercalcemia abnormally increased blood levels of calcium

hypercapnia abnormally elevated blood levels of CO_2

hyperchloremia higher-than-normal blood chloride levels

hyperkalemia higher-than-normal blood potassium levels

hypernatremia abnormal increase in blood sodium levels

hyperphosphatemia abnormally increased blood phosphate levels

hypocalcemia abnormally low blood levels of calcium

hypocapnia abnormally low blood levels of CO_2

hypochloremia lower-than-normal blood chloride levels

hypokalemia abnormally decreased blood levels of potassium

hyponatremia lower-than-normal levels of sodium in the blood

hypophosphatemia abnormally low blood phosphate levels

interstitial fluid (IF) fluid in the small spaces between cells not contained within blood vessels

intracellular fluid (ICF) fluid in the cytosol of cells

metabolic acidosis condition wherein a deficiency of bicarbonate causes the blood to be overly acidic

metabolic alkalosis condition wherein an excess of bicarbonate causes the blood to be overly alkaline

plasma osmolality ratio of solutes to a volume of solvent in the plasma; plasma osmolality reflects a person's state of hydration

respiratory acidosis condition wherein an excess of carbonic acid or CO_2 causes the blood to be overly acidic

respiratory alkalosis condition wherein a deficiency of carbonic acid/CO_2 levels causes the blood to be overly alkaline

Chapter Review

26.1 Body Fluids and Fluid Compartments

Your body is mostly water. Body fluids are aqueous solutions with differing concentrations of materials, called solutes. An appropriate balance of water and solute concentrations must be maintained to ensure cellular functions. If the cytosol becomes too concentrated due to water loss, cell functions deteriorate. If the cytosol becomes too dilute due to water intake by cells, cell membranes can be damaged, and the cell can burst. Hydrostatic pressure is the force exerted by a fluid against a wall and causes movement of fluid between compartments. Fluid can also move between compartments along an osmotic gradient. Active transport processes require ATP to move some solutes against their concentration gradients between compartments. Passive transport of a molecule or ion depends on its ability to pass easily through the membrane, as well as the existence of a high to low concentration gradient.

26.2 Water Balance

Homeostasis requires that water intake and output be balanced. Most water intake comes through the digestive tract via liquids and food, but roughly 10 percent of water available to the body is generated at the end of aerobic respiration during cellular metabolism. Urine produced by the kidneys accounts for the largest amount of water leaving the body. The kidneys can adjust the concentration of the urine to reflect the body's water needs, conserving water if the body is dehydrated or making urine more dilute to expel excess water when necessary. ADH is a hormone that helps the body to retain water by increasing water reabsorption by the kidneys.

26.3 Electrolyte Balance

Electrolytes serve various purposes, such as helping to conduct electrical impulses along cell membranes in neurons and muscles, stabilizing enzyme structures, and releasing hormones from endocrine glands. The ions in plasma also contribute to the osmotic balance

11. How soon after drinking a large glass of water will a person start increasing their urine output?
a. 5 minutes
b. 30 minutes
c. 1 hour
d. 3 hours

12. Bone serves as a mineral reserve for which two ions?
a. sodium and potassium
b. calcium and phosphate
c. chloride and bicarbonate
d. calcium and bicarbonate

13. Electrolytes are lost mostly through _____.
a. renal function
b. sweating
c. feces
d. respiration

14. The major cation in extracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

15. The major cation in intracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

16. The major anion in extracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

17. Most of the body's calcium is found in _____.
a. teeth
b. bone
c. plasma
d. extracellular fluids

18. Abnormally increased blood levels of sodium are termed _____.
a. hyperkalemia
b. hyperchloremia
c. hypernatremia
d. hypercalcemia

19. The ion with the lowest blood level is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

20. Which two ions are most affected by aldosterone?
a. sodium and potassium
b. chloride and bicarbonate
c. calcium and phosphate
d. sodium and phosphate

21. Which of the following is the most important buffer inside red blood cells?
a. plasma proteins
b. hemoglobin
c. phosphate buffers
d. bicarbonate: carbonic acid buffer

22. Which explanation best describes why plasma proteins can function as buffers?
a. Plasma proteins combine with bicarbonate to make a stronger buffer.
b. Plasma proteins are immune to damage from acids.
c. Proteins have both positive and negative charges on their surface.
d. Proteins are alkaline.

23. The buffer that is adjusted to control acid-base balance is _____.
a. plasma protein
b. hemoglobin
c. phosphate buffer
d. bicarbonate: carbonic acid buffer

24. Carbonic acid levels are controlled through the _____.
a. respiratory system
b. renal system
c. digestive system
d. metabolic rate of cells

25. Bicarbonate ion concentrations in the blood are controlled through the _____.
a. respiratory system
b. renal system
c. digestive system
d. metabolic rate of cells

26. Which reaction is catalyzed by carbonic anhydrase?
a. $HPO_4^{2-} + H^+ \leftrightarrow H_2PO_4^-$
b. $CO_2 + H_2O \leftrightarrow H_2CO_3$
c. $H_2PO_4^- + OH^- \leftrightarrow HPO_4^{2-} + H_2O$
d. $H_2CO_3 \leftrightarrow HCO_3^- + H^+$

27.1 Anatomy and Physiology of the Testicular Reproductive System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure and function of the organs of the testicular reproductive system
- Describe the structure and function of the sperm cell
- Explain the events during spermatogenesis that produce haploid sperm from diploid cells
- Identify the importance of testosterone in reproductive function

People often use the words "female" and "male" to describe two different concepts: our sense of gender identity, and our biological sex as determined by our X/Y chromosomes, hormones, sex organs, and other physical characteristics. For some people, gender identity is different from biological sex or their sex assigned at birth. In this chapter and the next chapter, "female" and "male" refer to sex only, and the typical reproductive anatomy of XX and XY individuals is discussed.

Unique for its role in reproduction, a **gamete** is a specialized sex cell, which in humans carries 23 chromosomes—one half the number in body cells. In almost all sexually reproducing species, these two haploid cells differ in size; the smaller gamete is called the male gamete and the larger one is called the female gamete. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male, or testicular, reproductive system (Figure 27.2) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In male humans, the most important androgen is testosterone. For people with a penis, several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which may deliver sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

scrotum has a raised medial thickening on the surface called the raphae.

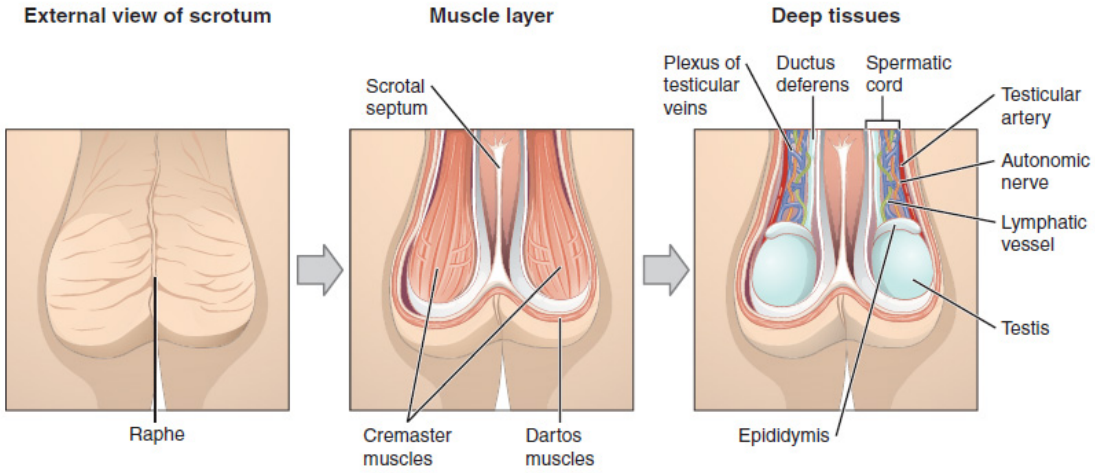


FIGURE 27.3 **The Scrotum and Testes** This anterior view shows the structures of the scrotum and testes.

Testes

The **testes** (singular = testis) are the male **gonads**—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan.

Paired ovals, adult testes are each approximately 4 to 5 cm in length and are housed within the scrotum (see Figure 27.3). They are surrounded by two distinct layers of protective connective tissue (Figure 27.4). The outer tunica vaginalis is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the tunica albuginea, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the “descent of the testis.” Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

27.4). The process begins at puberty, after which time sperm are produced constantly throughout a male's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a person produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia (Figure 27.5). Because these cells are diploid (2*n*), they each have a complete copy of the person's genetic material, or 46 chromosomes. However, mature gametes are haploid (1*n*), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

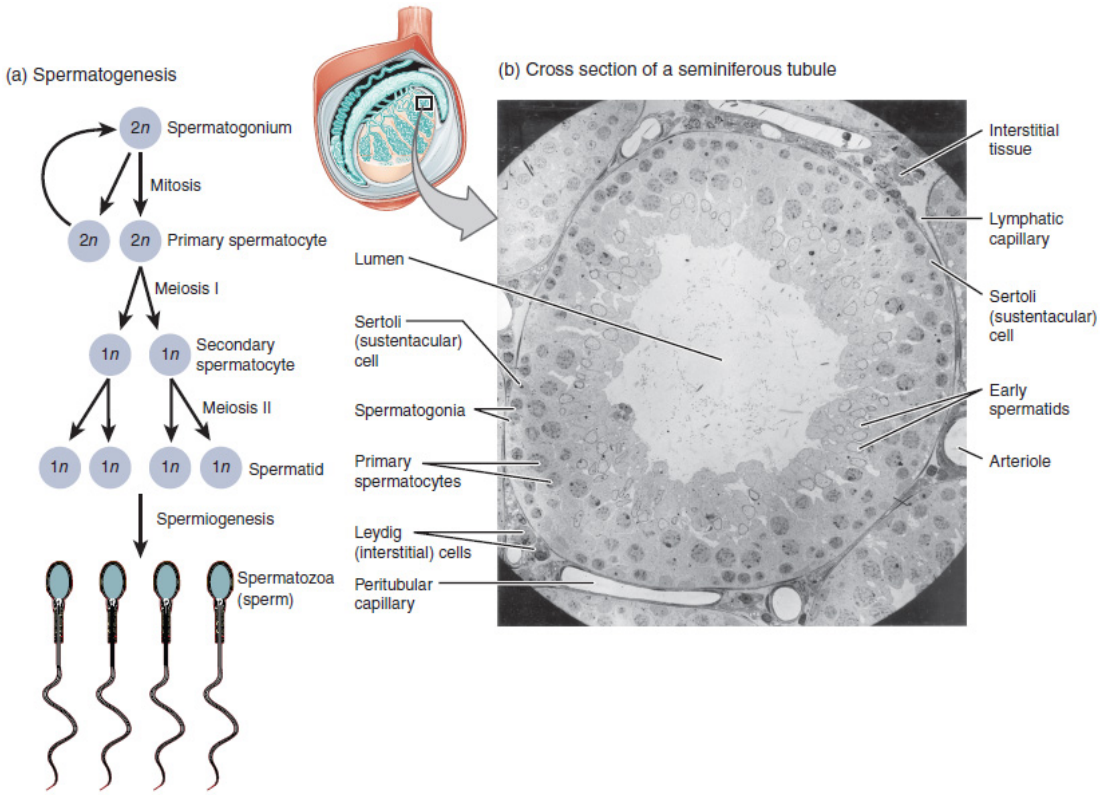


FIGURE 27.5 Spermatogenesis (a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary **spermatocyte**, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, before it undergoes a cell division called meiosis I. During meiosis I each of the 23 pairs of chromosomes separates. This results in two cells, called secondary spermatocytes, each with only half the number of chromosomes. Now a second round of cell division (meiosis II) occurs in both of the secondary spermatocytes. During meiosis II each of the 23 replicated chromosomes divides, similar to what happens during mitosis. Thus, meiosis results in separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a **spermatid**. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called **spermiogenesis** transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

INTERACTIVE LINK

Interactive Link Feature

Watch this video (http://openstax.org/l/vasectomy) to learn about a vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the person has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the **inguinal canal** in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning "flask").

Sperm make up only 5 percent of the final volume of **semen**, the thick, milky fluid that is ejaculated. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

Seminal Vesicles

As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated **seminal vesicle** (see Figure 27.2). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated **ejaculatory duct**, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

Prostate Gland

As shown in Figure 27.2, the centrally located **prostate gland** sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract.

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of males have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in males. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

Bulbourethral Glands

The final addition to semen is made by two **bulbourethral glands** (or Cowper's glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the

over the glans and forms a collar called the **prepuce** (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.

Disorders of the...

Male Reproductive System

Erectile dysfunction (ED) is a condition in which a person has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in males at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by **Leydig cells**. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and

testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Aging and the...

Male Reproductive System

Declines in Leydig cell activity can occur in males beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, people with this condition report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly males; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

27.2 Anatomy and Physiology of the Ovarian Reproductive System

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure and function of the organs of the ovarian reproductive system
- List the steps of oogenesis
- Describe the hormonal changes that occur during the ovarian and menstrual cycles
- Trace the path of an oocyte from ovary to fertilization

The female, or ovarian, reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity (Figure 27.9). Recall that the ovaries are the female gonads. The gamete they produce is called an **oocyte**. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.

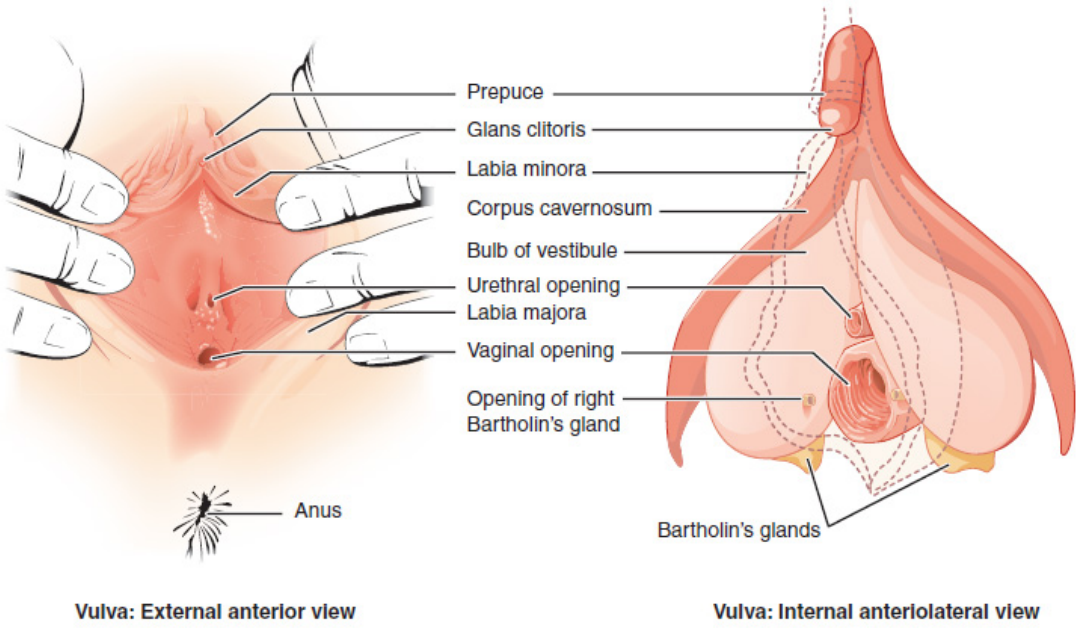


FIGURE 27.10 The Vulva The external female genitalia are referred to collectively as the vulva.

Vagina

The **vagina**, shown at the bottom of Figure 27.9 and Figure 27.10, is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae**. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy person, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that people do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

Ovaries

The **ovaries** are the female gonads (see Figure 27.9). Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the **broad ligament**. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by

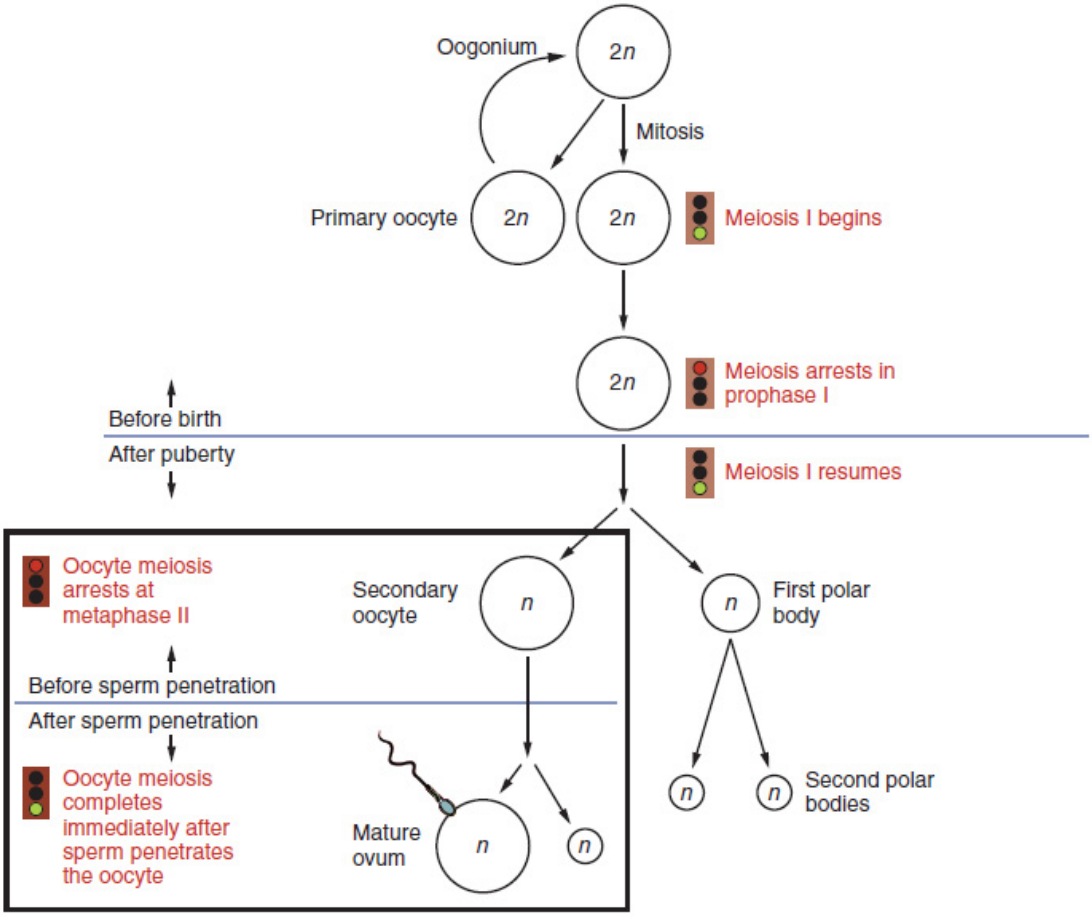


FIGURE 27.11 Oogenesis The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.

How does the diploid secondary oocyte become an **ovum**—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of egg-derived origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your biological mother, her mother, and so on back through your female ancestors.

Everyday Connection

Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from one parent, and half from the other parent. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. Our mother received mtDNA from their mother, who got it from their mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

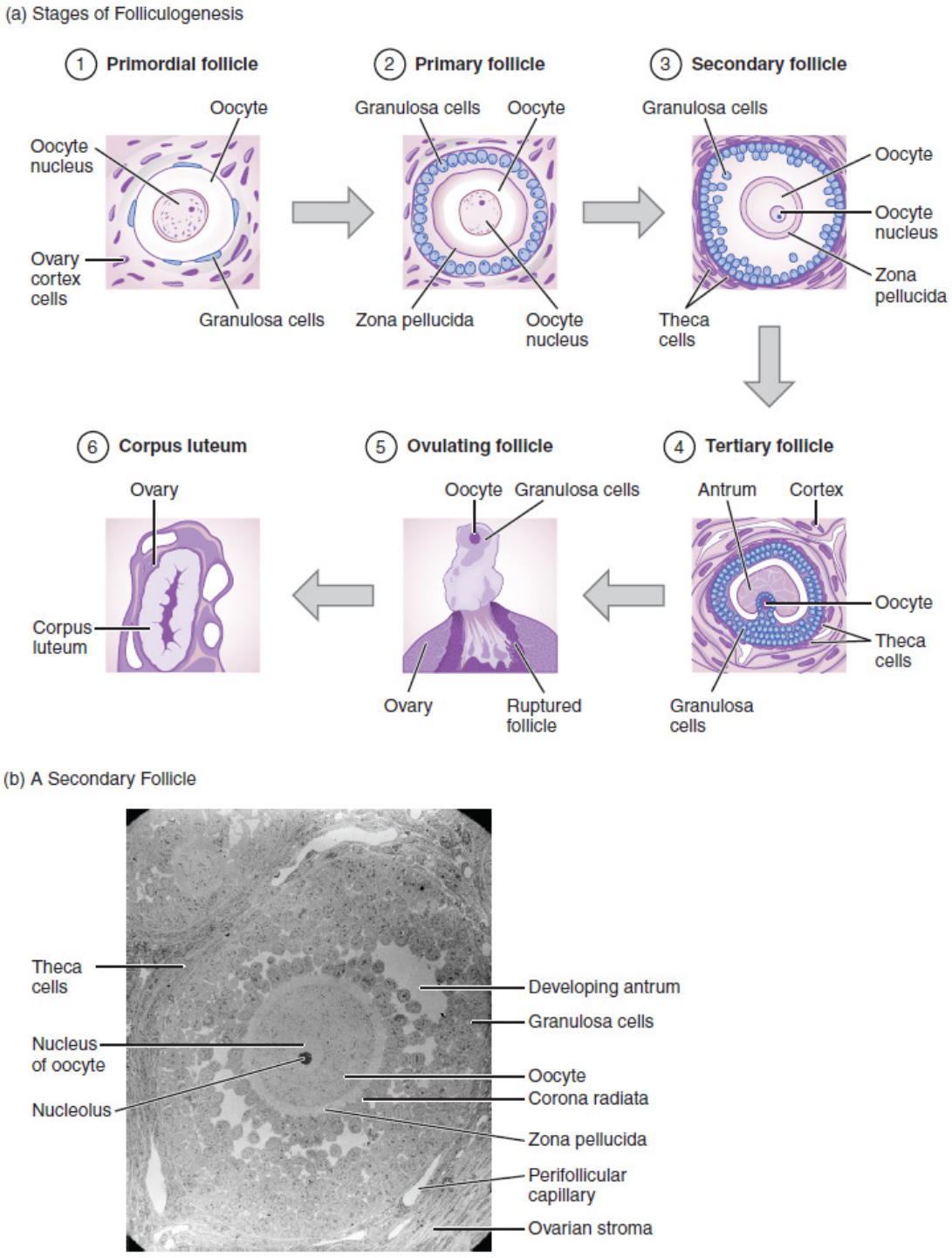


FIGURE 27.12 **Folliculogenesis** (a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Hormonal Control of the Ovarian Cycle

The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

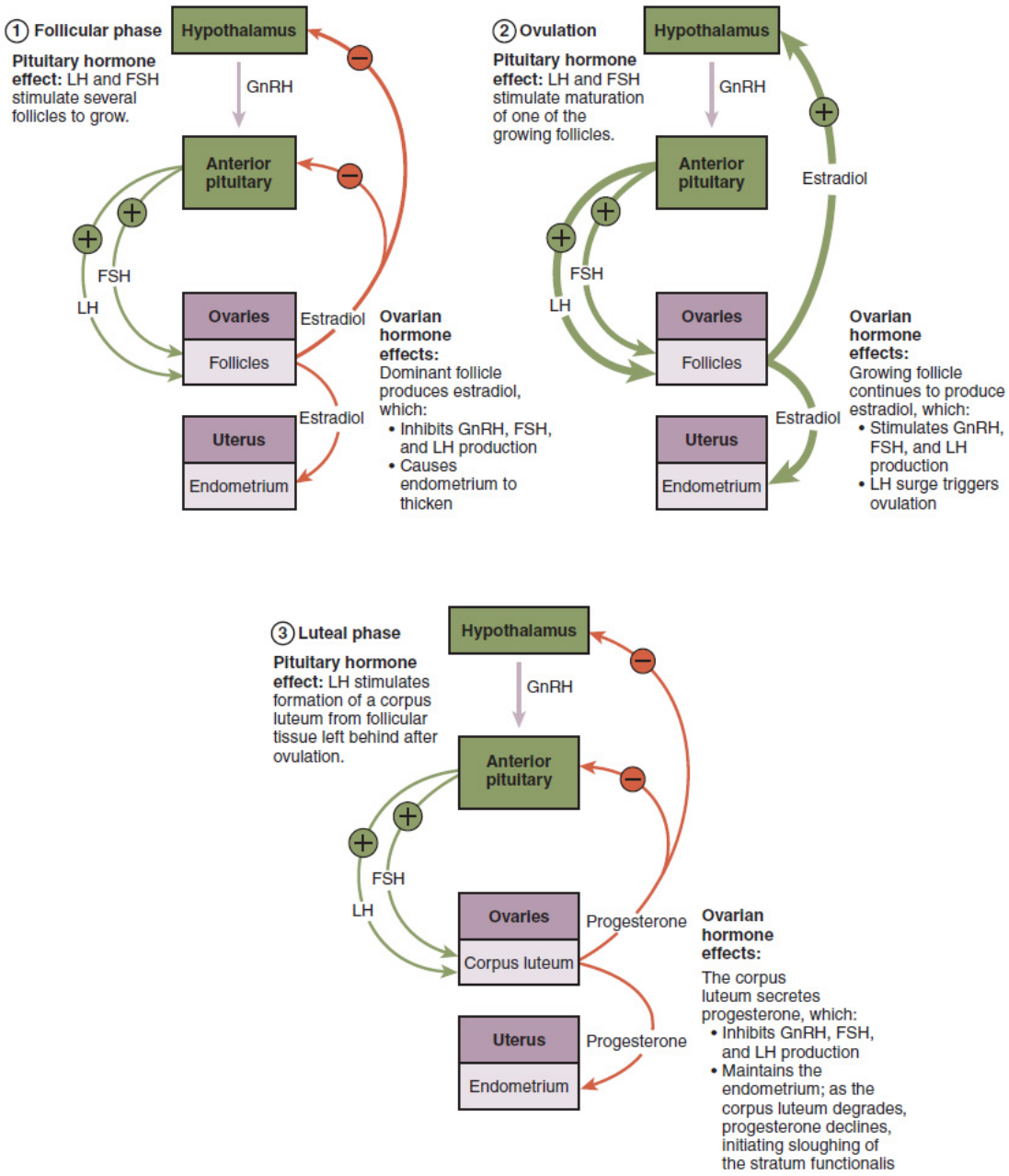


FIGURE 27.13 Hormonal Regulation of Ovulation The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.

When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn't occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (see Figure 27.13). The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity.

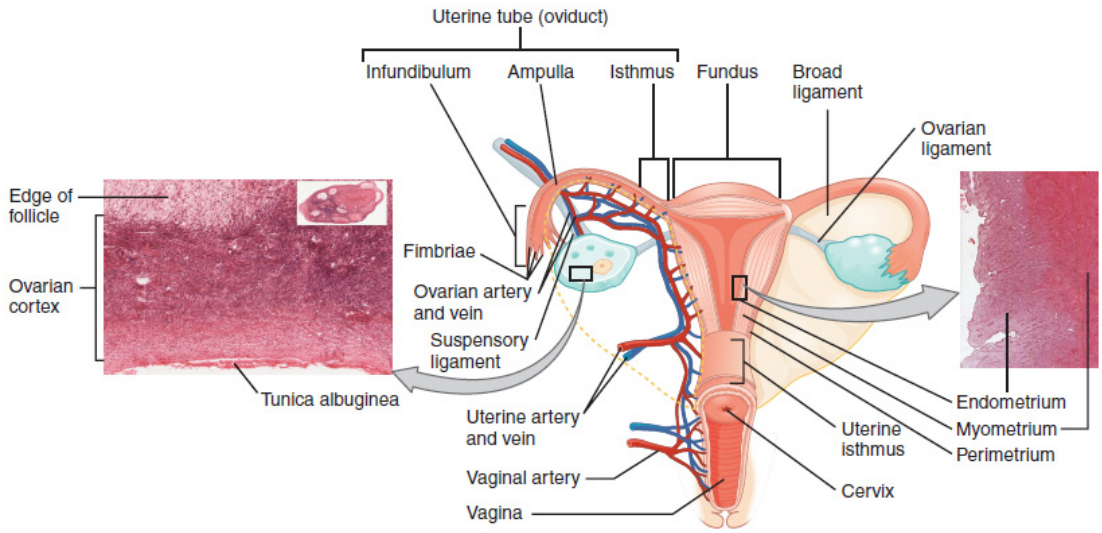


FIGURE 27.14 Ovaries, Uterine Tubes, and Uterus This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a person's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

INTERACTIVE LINK

Interactive Link

Watch this series of videos (http://openstax.org/l/oocyte) to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

The Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (see Figure 27.14). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the **body of uterus** (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or **perimetrium**, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or **myometrium**, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman’s period. Anteriorly directed myometrial contractions also occur near the time of ovulation,

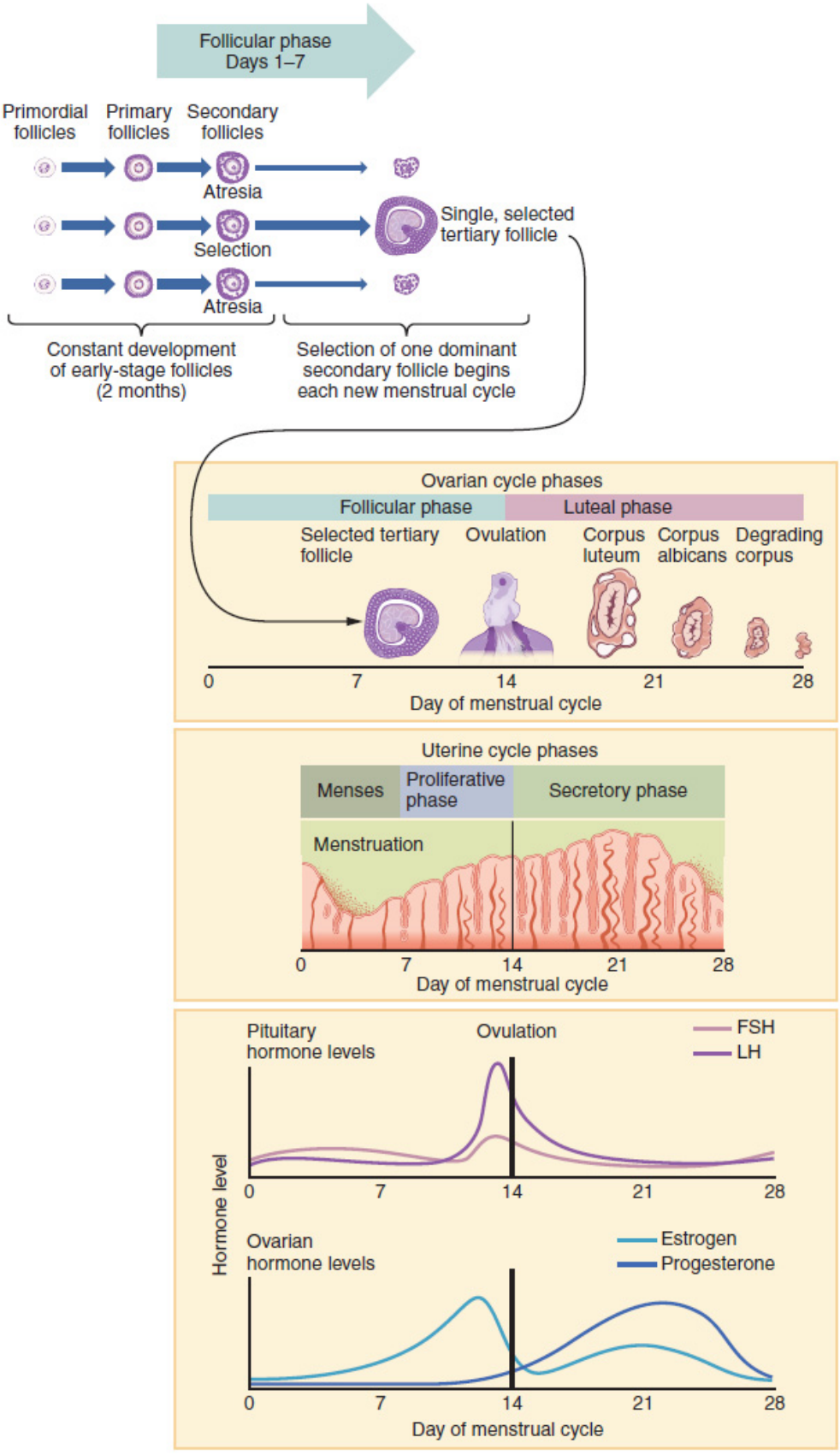


FIGURE 27.15 Hormone Levels in Ovarian and Menstrual Cycles The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

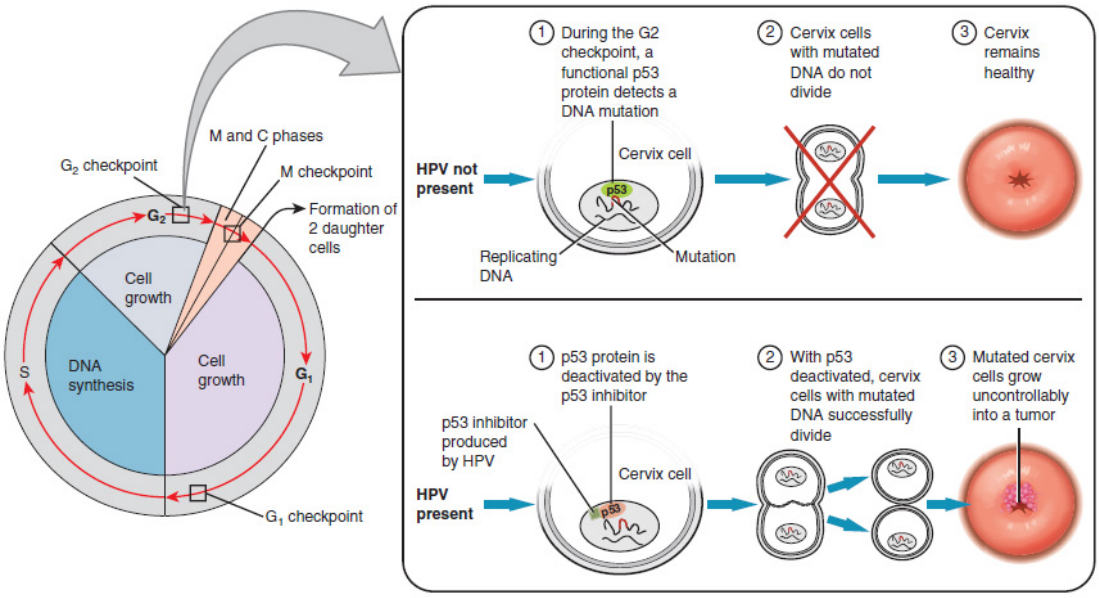


FIGURE 27.16 Development of Cervical Cancer In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, people in lower-income countries often do not have access to regular pap smears. As a result, these females in lower-income countries account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for females, because HPV is sexually transmitted, all people require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many people worldwide.

The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** (Figure 27.17), whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (see Figure 27.17). The clusters can change in size depending on the

hormones that they produce. Menopause is considered complete if an individual has not menstruated in a full year. After that point, they are considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur at any time in a person's forties or fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As the age of menopause approaches, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a mestrual cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in females as in males, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many people find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women’s Health Initiative began a study to observe for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when people first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that people on HT have regular pelvic and breast exams.

27.3 Development of the Male and Female Reproductive Systems

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Explain how bipotential tissues are directed to develop into male or female sex organs
- Name the rudimentary duct systems in the embryo that are precursors to male or female internal sex organs
- Describe the hormonal changes that bring about puberty, and the secondary sex characteristics

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in females, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In females who are extremely lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

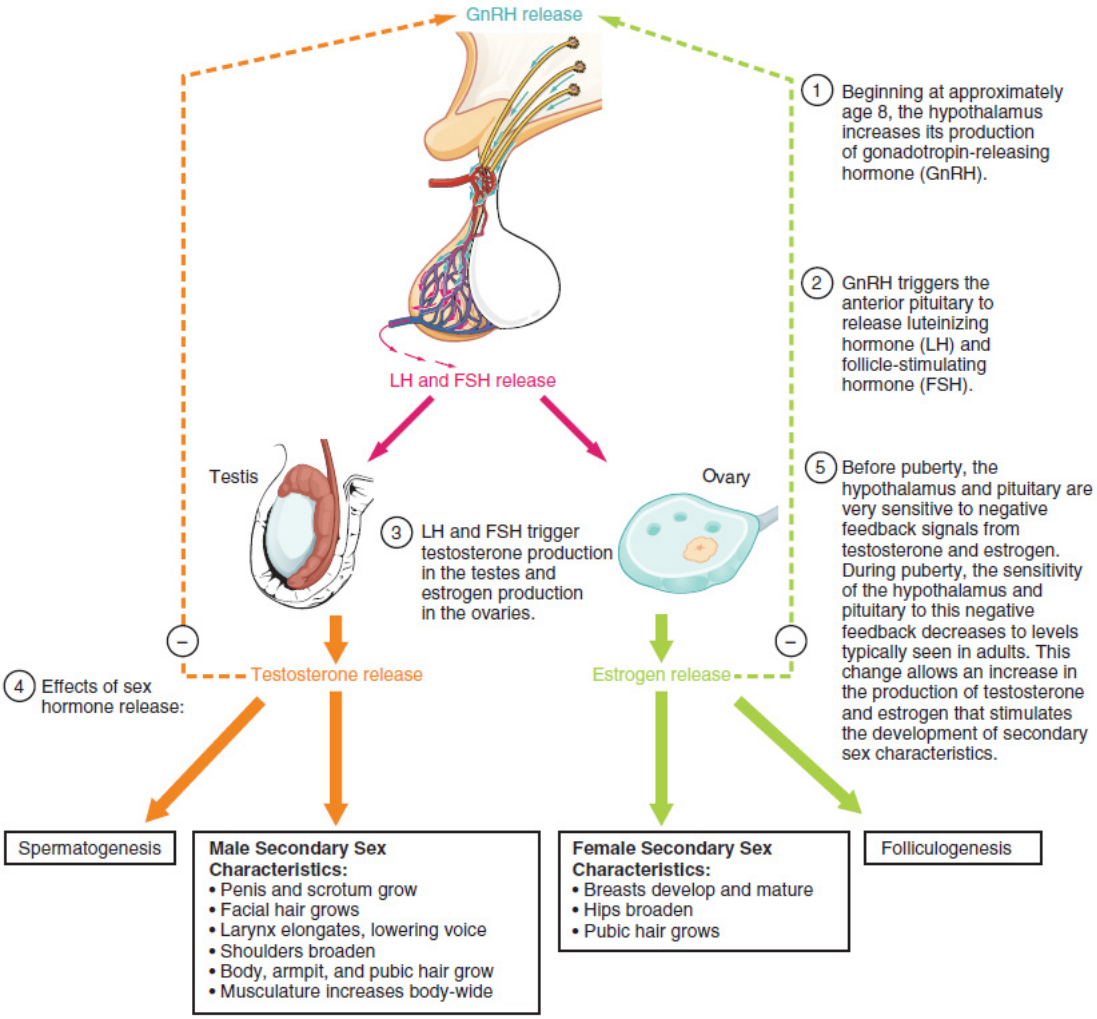


FIGURE 27.18 Hormones of Puberty During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.

Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in Table 27.1.

Key Terms

alveoli (of the breast) milk-secreting cells in the mammary gland
ampulla (of the uterine tube) middle portion of the uterine tube in which fertilization often occurs
antrum fluid-filled chamber that characterizes a mature tertiary (antral) follicle
areola highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling
Bartholin's glands (also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands
blood–testis barrier tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm
body of uterus middle section of the uterus
broad ligament wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall
bulbourethral glands (also, Cowper's glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation
cervix elongate inferior end of the uterus where it connects to the vagina
clitoris (also, glans clitoris) nerve-rich area of the vulva that contributes to sexual sensation during intercourse
corpus albicans nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum
corpus cavernosum either of two columns of erectile tissue in the penis that fill with blood during an erection
corpus luteum transformed follicle after ovulation that secretes progesterone
corpus spongiosum (plural = corpora cavernosa) column of erectile tissue in the penis that fills with blood during an erection and surrounds the penile urethra on the ventral portion of the penis
ductus deferens (also, vas deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens
ejaculatory duct duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra
endometrium inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses
epididymis (plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation
fimbriae fingerlike projections on the distal uterine tubes
follicle ovarian structure of one oocyte and surrounding granulosa (and later theca) cells
folliculogenesis development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins
fundus (of the uterus) domed portion of the uterus that is superior to the uterine tubes
gamete haploid reproductive cell that contributes genetic material to form an offspring
glans penis bulbous end of the penis that contains a large number of nerve endings
gonadotropin-releasing hormone (GnRH) hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland
gonads reproductive organs (testes and ovaries) that produce gametes and reproductive hormones
granulosa cells supportive cells in the ovarian follicle that produce estrogen
hymen membrane that covers part of the opening of the vagina
infundibulum (of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae
inguinal canal opening in abdominal wall that connects the testes to the abdominal cavity
isthmus narrow, medial portion of the uterine tube that joins the uterus
labia majora hair-covered folds of skin located behind the mons pubis
labia minora thin, pigmented, hairless flaps of skin located medial and deep to the labia majora
lactiferous ducts ducts that connect the mammary glands to the nipple and allow for the transport of milk
lactiferous sinus area of milk collection between alveoli and lactiferous duct
Leydig cells cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell
mammary glands glands inside the breast that secrete milk
menarche first menstruation in a pubertal female
menses shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation
menses phase phase of the menstrual cycle in which

uterus for the insertion of semen and from the uterus for the birth of a baby

vulva external female genitalia

Wolffian duct duct system present in the embryo that will eventually form the internal male reproductive structures

Chapter Review

27.1 Anatomy and Physiology of the Testicular Reproductive System

Gametes are the reproductive cells that combine to form offspring. Organs called gonads produce the gametes, along with the hormones that regulate human reproduction. The male gametes are called sperm. Spermatogenesis, the production of sperm, occurs within the seminiferous tubules that make up most of the testis. The scrotum is the muscular sac that holds the testes outside of the body cavity.

Spermatogenesis begins with mitotic division of spermatogonia (stem cells) to produce primary spermatocytes that undergo the two divisions of meiosis to become secondary spermatocytes, then the haploid spermatids. During spermiogenesis, spermatids are transformed into spermatozoa (formed sperm). Upon release from the seminiferous tubules, sperm are moved to the epididymis where they continue to mature. During ejaculation, sperm exit the epididymis through the ductus deferens, a duct in the spermatic cord that leaves the scrotum. The ampulla of the ductus deferens meets the seminal vesicle, a gland that contributes fructose and proteins, at the ejaculatory duct. The fluid continues through the prostatic urethra, where secretions from the prostate are added to form semen. These secretions help the sperm to travel through the urethra and into the female reproductive tract. Secretions from the bulbourethral glands protect sperm and cleanse and lubricate the penile (spongy) urethra.

The penis is the male organ of copulation. Columns of erectile tissue called the corpora cavernosa and corpus spongiosum fill with blood when sexual arousal activates vasodilatation in the blood vessels of the penis. Testosterone regulates and maintains the sex organs and sex drive, and induces the physical changes of puberty. Interplay between the testes and the endocrine system precisely control the production of testosterone with a negative feedback loop.

27.2 Anatomy and Physiology of the Ovarian Reproductive System

The external female genitalia are collectively called the vulva. The vagina is the pathway into and out of the uterus. The penis is inserted into the vagina to deliver sperm, and the baby exits the uterus through the vagina during childbirth.

The ovaries produce oocytes, the female gametes, in a process called oogenesis. As with spermatogenesis, meiosis produces the haploid gamete (in this case, an ovum); however, it is completed only in an oocyte that has been penetrated by a sperm. In the ovary, an oocyte surrounded by supporting cells is called a follicle. In folliculogenesis, primordial follicles develop into primary, secondary, and tertiary follicles. Early tertiary follicles with their fluid-filled antrum will be stimulated by an increase in FSH, a gonadotropin produced by the anterior pituitary, to grow in the 28-day ovarian cycle. Supporting granulosa and theca cells in the growing follicles produce estrogens, until the level of estrogen in the bloodstream is high enough that it triggers negative feedback at the hypothalamus and pituitary. This results in a reduction of FSH and LH, and most tertiary follicles in the ovary undergo atresia (they die). One follicle, usually the one with the most FSH receptors, survives this period and is now called the dominant follicle. The dominant follicle produces more estrogen, triggering positive feedback and the LH surge that will induce ovulation. Following ovulation, the granulosa cells of the empty follicle luteinize and transform into the progesterone-producing corpus luteum. The ovulated oocyte with its surrounding granulosa cells is picked up by the infundibulum of the uterine tube, and beating cilia help to transport it through the tube toward the uterus. Fertilization occurs within the uterine tube, and the final stage of meiosis is completed.

The uterus has three regions: the fundus, the body, and the cervix. It has three layers: the outer perimetrium, the muscular myometrium, and the inner endometrium. The endometrium responds to estrogen released by the follicles during the menstrual cycle and grows thicker with an increase in blood vessels in preparation for pregnancy. If the egg is not fertilized, no signal is sent to extend the life of the corpus luteum, and it degrades, stopping progesterone production. This decline in progesterone results in the sloughing of the inner portion of the endometrium in a process called menses, or menstruation.

The breasts are accessory organs that may be utilized after the birth of a child to produce milk in a process called lactation. Birth control pills provide constant levels of estrogen and progesterone to negatively feed

10. Spermatogenesis takes place in the _____.
   a. prostate gland
   b. glans penis
   c. seminiferous tubules
   d. ejaculatory duct

11. What are the female gonads called?
   a. oocytes
   b. ova
   c. oviducts
   d. ovaries

12. When do the oogonia undergo mitosis?
   a. before birth
   b. at puberty
   c. at the beginning of each menstrual cycle
   d. during fertilization

13. From what structure does the corpus luteum originate?
   a. uterine corpus
   b. dominant follicle
   c. fallopian tube
   d. corpus albicans

14. Where does fertilization of the egg by the sperm typically occur?
   a. vagina
   b. uterus
   c. uterine tube
   d. ovary

15. Why do estrogen levels fall after menopause?
   a. The ovaries degrade.
   b. There are no follicles left to produce estrogen.
   c. The pituitary secretes a menopause-specific hormone.
   d. The cells of the endometrium degenerate.

16. The vulva includes the _____.
   a. lactiferous duct, rugae, and hymen
   b. lactiferous duct, endometrium, and bulbourethral glands
   c. mons pubis, endometrium, and hymen
   d. mons pubis, labia majora, and Bartholin's glands

17. What controls whether an embryo will develop testes or ovaries?
   a. pituitary gland
   b. hypothalamus
   c. Y chromosome
   d. presence or absence of estrogen

18. Without *SRY* expression, an embryo will develop _____.
   a. male reproductive structures
   b. female reproductive structures
   c. no reproductive structures
   d. male reproductive structures 50 percent of the time and female reproductive structures 50 percent of the time

19. The timing of puberty can be influenced by which of the following?
   a. genes
   b. stress
   c. amount of body fat
   d. all of the above

Critical Thinking Questions

20. Briefly explain why mature gametes carry only one set of chromosomes.

21. What special features are evident in sperm cells but not in somatic cells, and how do these specializations function?

22. What do each of the three male accessory glands contribute to the semen?

23. Describe how penile erection occurs.

24. While anabolic steroids (synthetic testosterone) bulk up muscles, they can also affect testosterone production in the testis. Using what you know about negative feedback, describe what would happen to testosterone production in the testis if a male takes large amounts of synthetic testosterone.

25. Follow the path of ejaculated sperm from the vagina to the oocyte. Include all structures of the female reproductive tract that the sperm must travel through to reach the egg.

26. Identify some differences between meiosis in males and females.

27. Explain the hormonal regulation of the phases of the menstrual cycle.

28. Endometriosis is a disease characterized by the presence of endometrial-like tissue found outside the uterus—in the uterine tubes, on the ovaries, or even in the pelvic cavity. Offer a hypothesis as to why endometriosis increases a woman's risk of infertility.

reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell, called a **zygote**, contains all of the genetic material needed to form a human—half from each biological parent.

Transit of Sperm

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the acidity of the vagina (approximately pH 3.8), and millions more may be blocked from entering the uterus by thick cervical mucus. Of those that do enter, thousands are destroyed by phagocytic uterine leukocytes. Thus, the race into the uterine tubes, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called **capacitation**, or priming. The fluids improve the motility of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm, thinning the membrane in such a way that will help facilitate the release of the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte's exterior once contact is made. Sperm must undergo the process of capacitation in order to have the "capacity" to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte's thick outer layer of cells.

Contact Between Sperm and Oocyte

Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized oocyte cannot survive the 72-hour journey to the uterus. As you will recall from your study of the oogenesis, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The **corona radiata** is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying **zona pellucida** (pellucid = "transparent") is a transparent, but thick, glycoprotein membrane that surrounds the cell's plasma membrane.

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the **acrosomal reaction** in which the enzyme-filled "cap" of the sperm, called the **acrosome**, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte's plasma membrane (Figure 28.2). The plasma membrane of that sperm then fuses with the oocyte's plasma membrane, and the head and mid-piece of the "winning" sperm enter the oocyte interior.

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes released by this reaction digest the extracellular matrix of the corona radiata. As you can see, the first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte. If you consider the loss of millions of sperm between entry into the vagina and degradation of the zona pellucida, you can understand why a low sperm count can cause male infertility.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a chorionic cavity.

Everyday Connection

In Vitro Fertilization

IVF, which stands for in vitro fertilization, is an assisted reproductive technology. In vitro, which in Latin translates to "in glass," refers to a procedure that takes place outside of the body. There are many different indications for IVF. The procedure is used frequently in supporting LGBTQ people, people using surrogates/gestational carriers, and also people who have difficulties reproducing. For example, a person may produce healthy eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A person may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

Next, the eggs and sperm are mixed in a petri dish. The ideal ratio is 75,000 sperm to one egg. If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman's uterus using a plastic catheter (tube). Figure 28.3 illustrates the steps involved in IVF.

28.2 Embryonic Development

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Distinguish the stages of embryonic development that occur before implantation
- Describe the process of implantation
- List and describe four embryonic membranes
- Explain gastrulation
- Describe how the placenta is formed and identify its functions
- Explain how an embryo transforms from a flat disc of cells into a three-dimensional shape resembling a human
- Summarize the process of organogenesis

Throughout this chapter, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period of time required for full development of a fetus in utero is referred to as **gestation** (gestare = "to carry" or "to bear"). It can be subdivided into distinct gestational periods. The first 2 weeks of prenatal development are referred to as the pre-embryonic stage. A developing human is referred to as an **embryo** during weeks 3–8, and a **fetus** from the ninth week of gestation until birth. In this section, we'll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.

Pre-implantation Embryonic Development

Following fertilization, the zygote and its associated membranes, together referred to as the **conceptus**, continue to be projected toward the uterus by peristalsis and beating cilia of the epithelial cells of the Fallopian tube. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each **cleavage** results in more cells, it does not increase the total volume of the conceptus (Figure 28.4). Each daughter cell produced by cleavage is called a **blastomere** (blastos = "germ," in the sense of a seed or sprout).

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the **morula** (morula = "little mulberry"). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells, and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the **blastocoel**. At this developmental stage, the conceptus is referred to as a **blastocyst**. Within this structure, a group of cells forms into an **inner cell mass**, which is fated to become the embryo. The cells that form the outer shell are called **trophoblasts** (trophe = "to feed" or "to nourish"). These cells will develop into the chorionic sac and the fetal portion of the **placenta** (the organ of nutrient, waste, and gas exchange between a pregnant person and the developing offspring).

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells' fates are set as being the precursors to a specific lineage of cells.

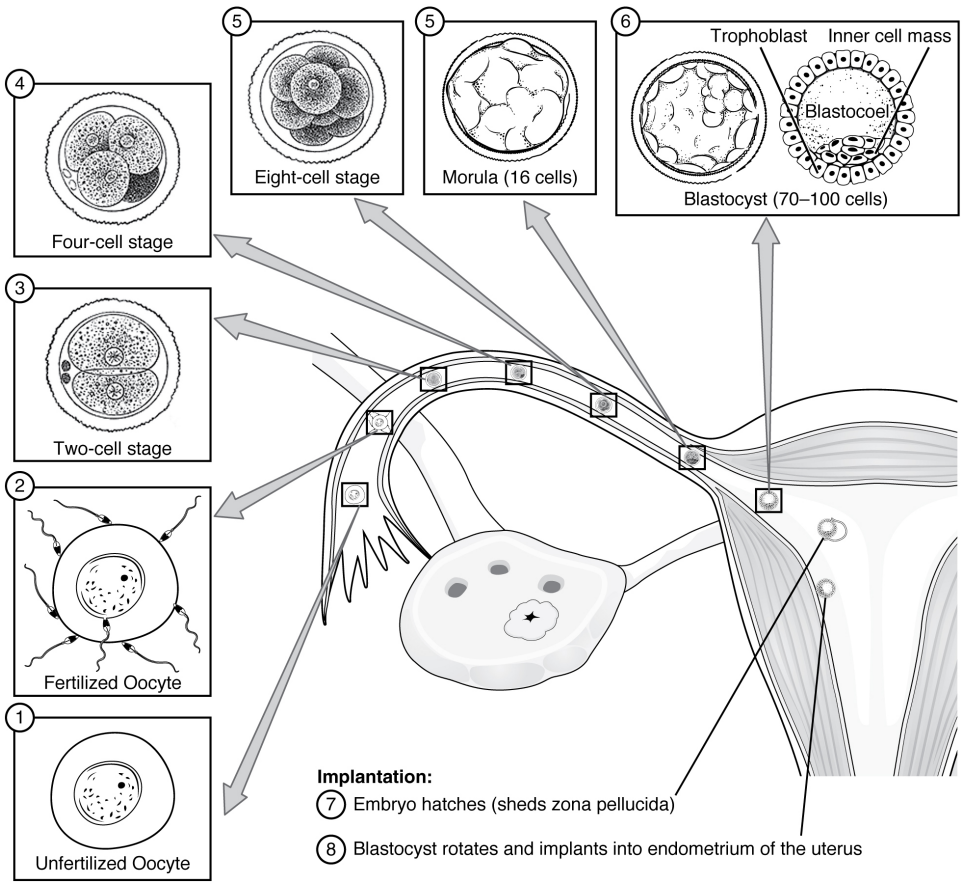


FIGURE 28.5 Pre-Embryonic Development Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse with each other, forming the **syncytiotrophoblast**, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst (Figure 28.6). The trophoblast secretes **human chorionic gonadotropin (hCG)**, a hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. Implantation is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.

which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was "lost" to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a tubal pregnancy re-implanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas' pouch), the mesentery of the intestines, and the greater omentum are some common sites.

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases "snagging" the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected early, the embryo's development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix (Figure 28.7). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).

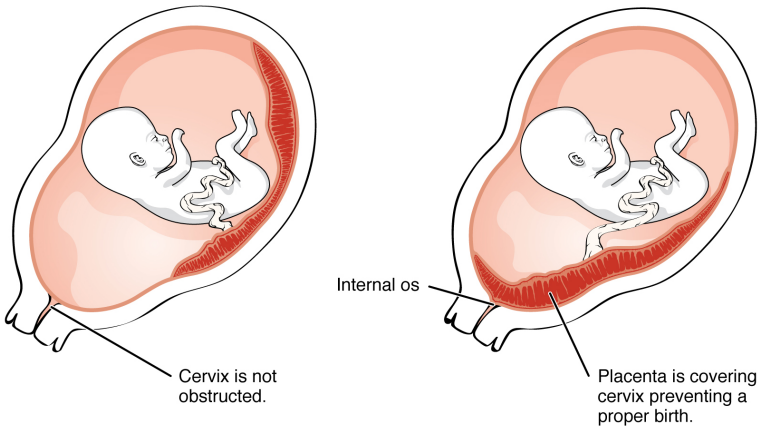


FIGURE 28.7 Placenta Previa An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix.

Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the **amniotic cavity**—opens up between it and the trophoblast (Figure 28.8). Cells from the upper layer of the disc (the **epiblast**) extend around the amniotic cavity, creating a membranous sac that forms into the **amnion** by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

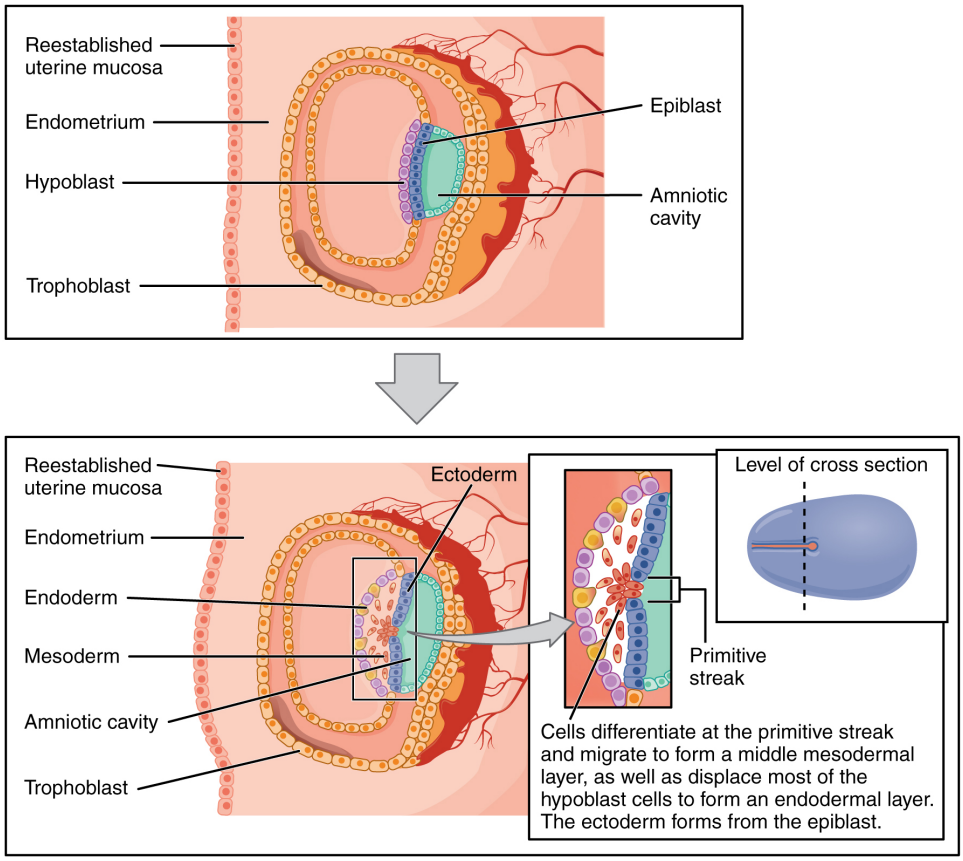


FIGURE 28.9 Germ Layers Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs (Figure 28.10).

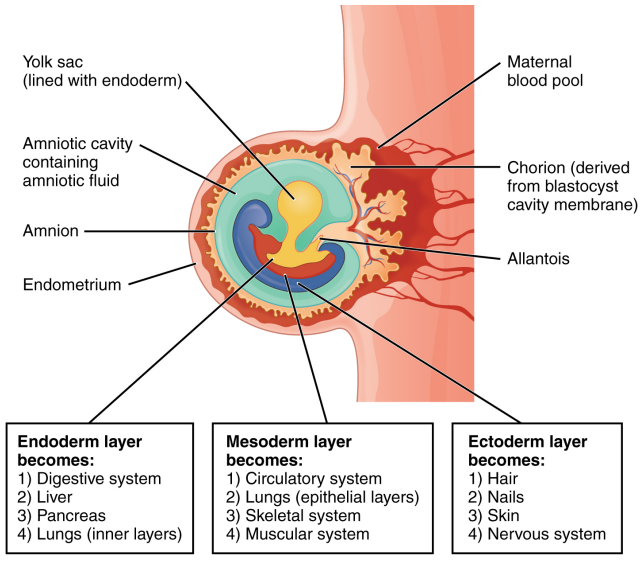


FIGURE 28.10 Fates of Germ Layers in Embryo Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant.

Although blood cells are not exchanged, the chorionic villi provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, barbiturates, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant people should avoid fetotoxic substances. Alcohol consumption by pregnant people, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as well as cognitive and behavioral disorders.

Functions of the Placenta

Nutrition and digestion	Respiration	Endocrine function
• Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals • Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy • Excretes and filters fetal nitrogenous wastes into maternal blood	• Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport	• Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development • Mediates the transmission of maternal hormones into fetal blood and vice versa

TABLE 28.1



FIGURE 28.12 **Placenta** This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side.

Organogenesis

Following gastrulation, rudiments of the central nervous system develop from the ectoderm in the process of **neurulation** (Figure 28.13). Specialized neuroectodermal tissues along the length of the embryo thicken into the **neural plate**. During the fourth week, tissues on either side of the plate fold upward into a **neural fold**. The two folds converge to form the **neural tube**. The tube lies atop a rod-shaped, mesoderm-derived **notochord**, which eventually becomes the nucleus pulposus of intervertebral discs. Block-like structures called **somites** form on either side of the tube, eventually differentiating into the axial skeleton, skeletal muscle, and dermis. During the fourth and fifth weeks, the anterior neural tube dilates and subdivides to form vesicles that will become the brain structures.

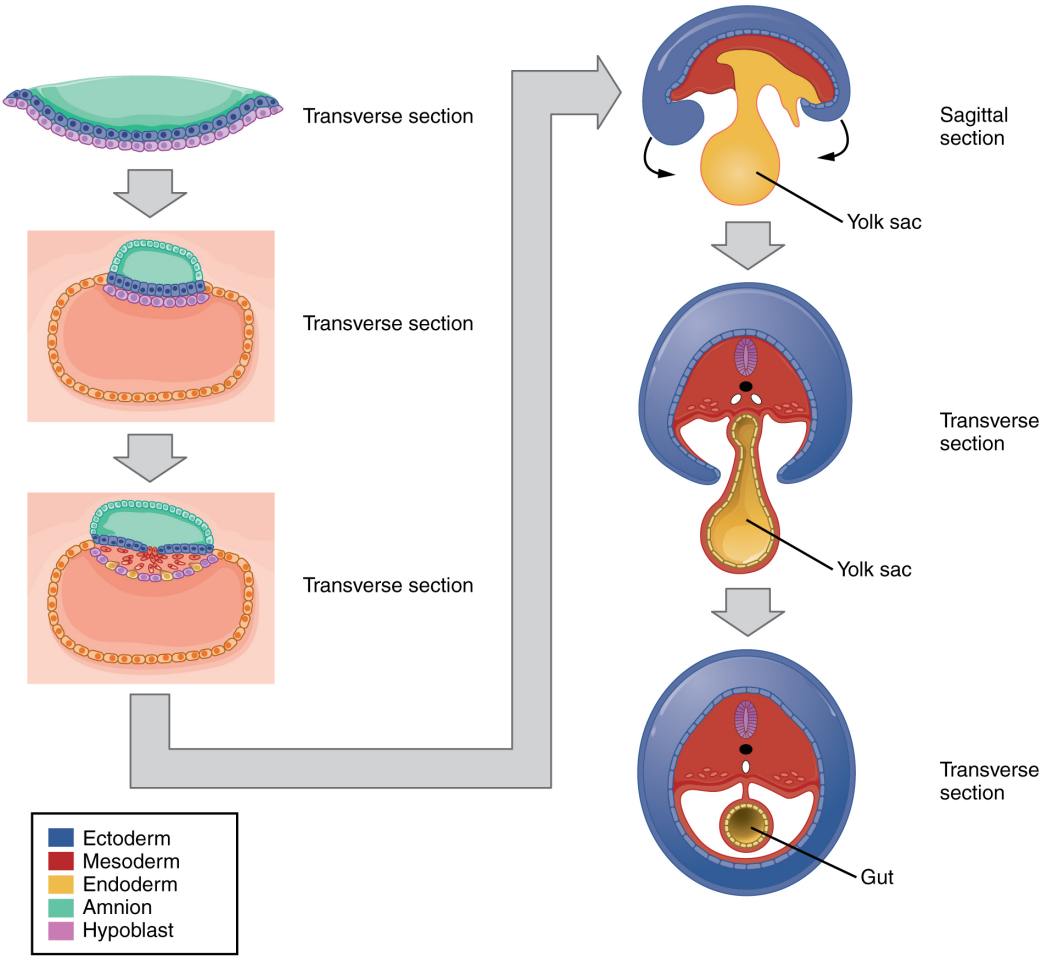


FIGURE 28.14 Embryonic Folding Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure.

Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called **organogenesis**.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.

During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate. By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses (Figure 28.15). By the eighth week, the head is nearly as large as the rest of the embryo's body, and all major brain structures are in place. The external genitalia are apparent, but at this point, male and female embryos are indistinguishable. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).

and a rectum.

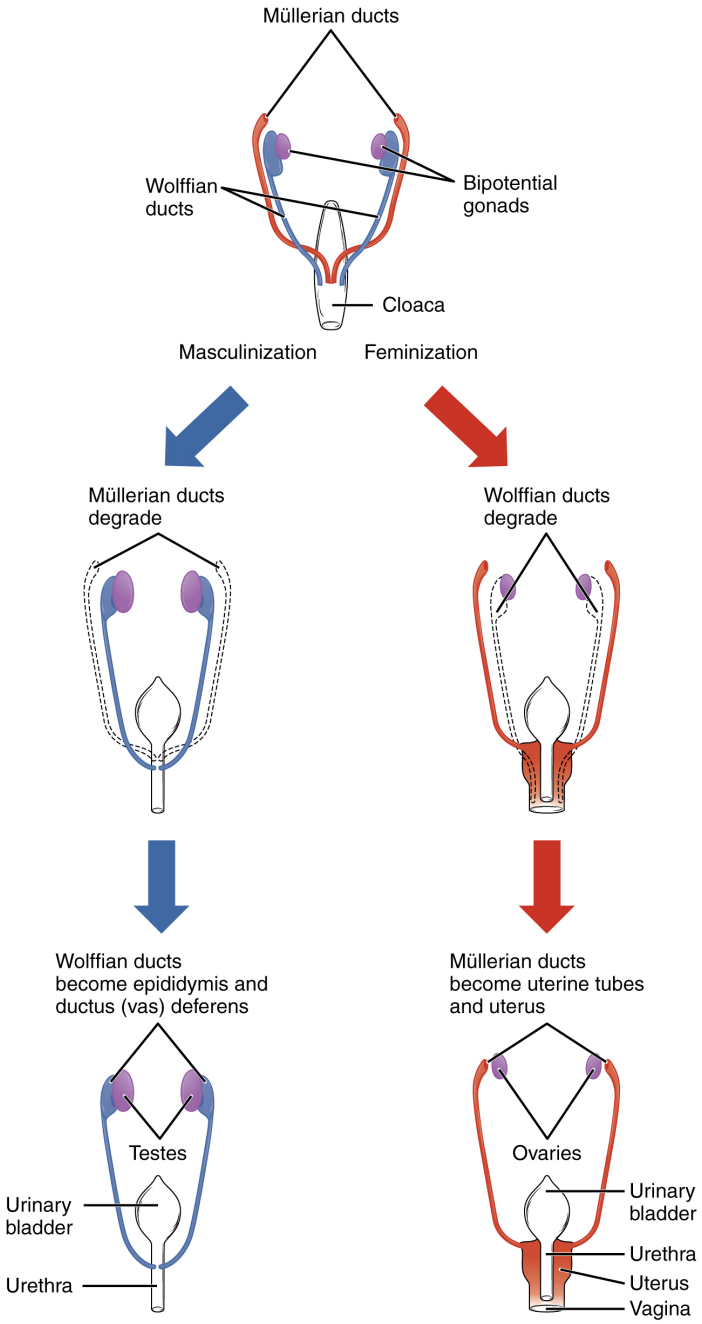


FIGURE 28.16 **Sexual Differentiation** Differentiation of the male and female reproductive systems does not occur until the fetal period of development.

The Fetal Circulatory System

During prenatal development, the fetal circulatory system is integrated with the placenta via the umbilical cord so that the fetus receives both oxygen and nutrients from the placenta. However, after childbirth, the umbilical cord is severed, and the newborn's circulatory system must be reconfigured. When the heart first forms in the embryo, it exists as two parallel tubes derived from mesoderm and lined with endothelium, which then fuse together. As the embryo develops into a fetus, the tube-shaped heart folds and further differentiates into the four chambers present in a mature heart. Unlike a mature cardiovascular system, however, the fetal cardiovascular system also includes circulatory shortcuts, or shunts. A **shunt** is an anatomical (or sometimes surgical) diversion that allows blood flow to bypass immature organs such as the lungs and liver until childbirth.

partially functioning organs, as well as blood supply to and from the placenta.

Other Organ Systems

During weeks 9–12 of fetal development, the brain continues to expand, the body elongates, and ossification continues. Fetal movements are frequent during this period, but are jerky and not well-controlled. The bone marrow begins to take over the process of erythrocyte production—a task that the liver performed during the embryonic period. The liver now secretes bile. The fetus circulates amniotic fluid by swallowing it and producing urine. The eyes are well-developed by this stage, but the eyelids are fused shut. The fingers and toes begin to develop nails. By the end of week 12, the fetus measures approximately 9 cm (3.5 in) from crown to rump.

Weeks 13–16 are marked by sensory organ development. The eyes move closer together; blinking motions begin, although the eyes remain sealed shut. The lips exhibit sucking motions. The ears move upward and lie flatter against the head. The scalp begins to grow hair. The excretory system is also developing: the kidneys are well-formed, and **meconium**, or fetal feces, begins to accumulate in the intestines. Meconium consists of ingested amniotic fluid, cellular debris, mucus, and bile.

During approximately weeks 16–20, as the fetus grows and limb movements become more powerful, the pregnant person may begin to feel **quickening**, or fetal movements. However, space restrictions limit these movements and typically force the growing fetus into the "fetal position," with the arms crossed and the legs bent at the knees. Sebaceous glands coat the skin with a waxy, protective substance called **vernix caseosa** that protects and moisturizes the skin and may provide lubrication during childbirth. A silky hair called **lanugo** also covers the skin during weeks 17–20, but it is shed as the fetus continues to grow. Extremely premature infants sometimes exhibit residual lanugo.

Developmental weeks 21–30 are characterized by rapid weight gain, which is important for maintaining a stable body temperature after birth. The bone marrow completely takes over erythrocyte synthesis, and the axons of the spinal cord begin to be myelinated, or coated in the electrically insulating glial cell sheaths that are necessary for efficient nervous system functioning. (The process of myelination is not completed until adolescence.) During this period, the fetus grows eyelashes. The eyelids are no longer fused and can be opened and closed. The lungs begin producing surfactant, a substance that reduces surface tension in the lungs and assists proper lung expansion after birth. Inadequate surfactant production in premature newborns may result in respiratory distress syndrome, and as a result, the newborn may require surfactant replacement therapy, supplemental oxygen, or maintenance in a continuous positive airway pressure (CPAP) chamber during their first days or weeks of life. In male fetuses, the testes descend into the scrotum near the end of this period. The fetus at 30 weeks measures 28 cm (11 in) from crown to rump and exhibits the approximate body proportions of a full-term newborn, but still is much leaner.

INTERACTIVE LINK

Visit this site (http://openstax.org/l/pregstages) for a summary of the stages of pregnancy, as experienced by the pregnant person, and view the stages of development of the fetus throughout gestation. At what point in fetal development can a regular heartbeat be detected?

The fetus continues to lay down subcutaneous fat from week 31 until birth. The added fat fills out the hypodermis, and the skin transitions from red and wrinkled to soft and pink. Lanugo is shed, and the nails grow to the tips of the fingers and toes. Immediately before birth, the average crown-to-rump length is 35.5–40.5 cm (14–16 in), and the fetus weighs approximately 2.5–4 kg (5.5–8.8 lbs). Once born, the newborn is no longer confined to the fetal position, so subsequent measurements are made from head-to-toe instead of from crown-to-rump. At birth, the average length is approximately 51 cm (20 in).

Disorders of the...

Developing Fetus

Throughout the second half of gestation, the fetal intestines accumulate a tarry, greenish black meconium. The newborn's first stools consist almost entirely of meconium; they later transition to seedy yellow stools or slightly formed tan stools as meconium is cleared and replaced with digested breast milk or formula, respectively.

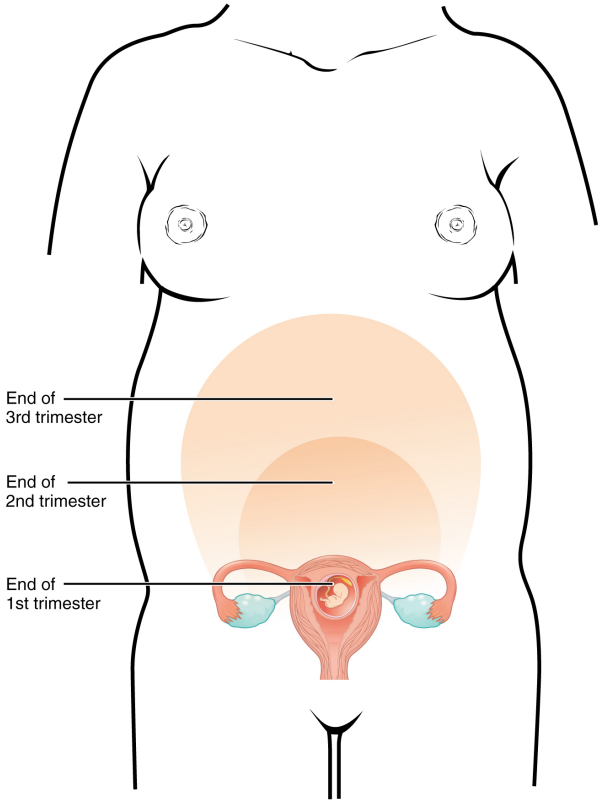


FIGURE 28.18 Size of Uterus throughout Pregnancy The uterus grows throughout pregnancy to accommodate the fetus.

Effects of Hormones

Virtually all of the effects of pregnancy can be attributed in some way to the influence of hormones—particularly estrogens, progesterone, and hCG. During weeks 7–12 from the LMP, the pregnancy hormones are primarily generated by the corpus luteum. Progesterone secreted by the corpus luteum stimulates the production of decidual cells of the endometrium that nourish the blastocyst before placentation. As the placenta develops and the corpus luteum degenerates during weeks 12–17, the placenta gradually takes over as the endocrine organ of pregnancy.

The placenta converts weak androgens secreted by the maternal and fetal adrenal glands to estrogens, which are necessary for pregnancy to progress. Estrogen levels climb throughout the pregnancy, increasing 30-fold by childbirth. Estrogens have the following actions:

- They suppress FSH and LH production, effectively preventing ovulation. (This function is the biological basis of hormonal birth control pills.)
- They induce the growth of fetal tissues and are necessary for the maturation of the fetal lungs and liver.
- They promote fetal viability by regulating progesterone production and triggering fetal synthesis of cortisol, which helps with the maturation of the lungs, liver, and endocrine organs such as the thyroid gland and adrenal gland.
- They stimulate maternal tissue growth, leading to uterine enlargement and mammary duct expansion and branching.

Relaxin, another hormone secreted by the corpus luteum and then by the placenta, helps prepare the body for childbirth. It increases the elasticity of the symphysis pubis joint and pelvic ligaments, making room for the growing fetus and allowing expansion of the pelvic outlet for childbirth. Relaxin also helps dilate the cervix during labor.

The placenta takes over the synthesis and secretion of progesterone throughout pregnancy as the corpus luteum degenerates. Like estrogen, progesterone suppresses FSH and LH. It also inhibits uterine contractions, protecting the fetus from preterm birth. This hormone decreases in late gestation, allowing uterine contractions to intensify and eventually progress to true labor. The placenta also produces hCG. In addition to promoting survival of the corpus luteum, hCG stimulates the male fetal gonads to secrete testosterone, which is essential for the

contribute to nausea. By about week 12 of pregnancy, nausea typically subsides.

A common gastrointestinal complaint during the later stages of pregnancy is gastric reflux, or heartburn, which results from the upward, constrictive pressure of the growing uterus on the stomach. The same decreased peristalsis that may contribute to nausea in early pregnancy is also thought to be responsible for pregnancy-related constipation as pregnancy progresses.

The downward pressure of the uterus also compresses the urinary bladder, leading to frequent urination. The problem is exacerbated by increased urine production. In addition, the maternal urinary system processes both maternal and fetal wastes, further increasing the total volume of urine.

Circulatory System Changes

Blood volume increases substantially during pregnancy, so that by childbirth, it exceeds its preconception volume by 30 percent, or approximately 1–2 liters. The greater blood volume helps to manage the demands of fetal nourishment and fetal waste removal. In conjunction with increased blood volume, the pulse and blood pressure also rise moderately during pregnancy. As the fetus grows, the uterus compresses underlying pelvic blood vessels, hampering venous return from the legs and pelvic region. As a result, many pregnant people develop varicose veins or hemorrhoids.

Respiratory System Changes

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50 percent to compensate for the oxygen demands of the fetus and the increased maternal metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each inspiration and potentially causing shortness of breath, or dyspnea. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus descends lower in a process called **lightening**. This typically ameliorates dyspnea.

The respiratory mucosa swell in response to increased blood flow during pregnancy, leading to nasal congestion and nose bleeds, particularly when the weather is cold and dry. Humidifier use and increased fluid intake are often recommended to counteract congestion.

Integumentary System Changes

The dermis stretches extensively to accommodate the growing uterus, breast tissue, and fat deposits on the thighs and hips. Torn connective tissue beneath the dermis can cause striae (stretch marks) on the abdomen, which appear as red or purple marks during pregnancy that fade to a silvery white color in the months after childbirth.

An increase in melanocyte-stimulating hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra (Figure 28.19). Melanin production during pregnancy may also darken or discolor skin on the face to create a chloasma, or “mask of pregnancy.”



FIGURE 28.19 Linea Nigra The linea nigra, a dark medial line running from the umbilicus to the pubis, forms during pregnancy and persists for a few weeks following childbirth. The linea nigra shown here corresponds to a pregnancy that is 22 weeks along.

may take minutes, hours, or days, depending in part on whether the person has given birth before; in each subsequent labor, this stage tends to be shorter.

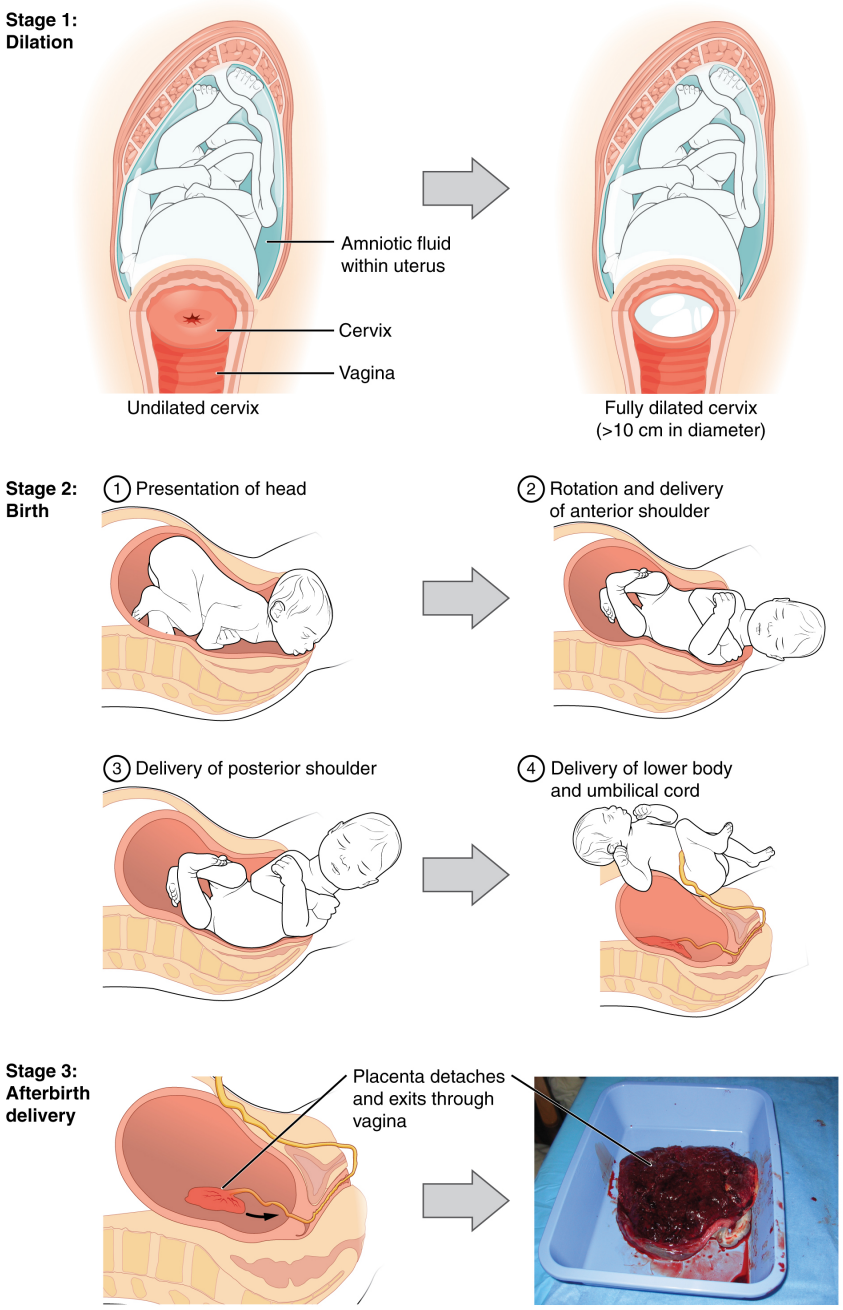


FIGURE 28.21 Stages of Childbirth The stages of childbirth include Stage 1, early cervical dilation; Stage 2, full dilation and expulsion of the newborn; and Stage 3, delivery of the placenta and associated fetal membranes. (The position of the newborn's shoulder is described relative to the person giving birth.)

True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal

28.5 Adjustments of the Infant at Birth and Postnatal Stages

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Discuss the importance of an infant's first breath
- Explain the closing of the cardiac shunts
- Describe thermoregulation in the newborn
- Summarize the importance of intestinal flora in the newborn

From a fetal perspective, the process of birth is a crisis. In the womb, the fetus was snuggled in a soft, warm, dark, and quiet world. The placenta provided nutrition and oxygen continuously. Suddenly, the contractions of labor and vaginal childbirth forcibly squeeze the fetus through the birth canal, limiting oxygenated blood flow during contractions and shifting the skull bones to accommodate the small space. After birth, the newborn's system must make drastic adjustments to a world that is colder, brighter, and louder, and where they will experience hunger and thirst. The neonatal period (neo- = "new"; -natal = "birth") spans the first to the thirtieth day of life outside of the uterus.

Respiratory Adjustments

Although the fetus "practices" breathing by inhaling amniotic fluid in utero, there is no air in the uterus and thus no true opportunity to breathe. (There is also no need to breathe because the placenta supplies the fetus with all the oxygenated blood it needs.) During gestation, the partially collapsed lungs are filled with amniotic fluid and exhibit very little metabolic activity. Several factors stimulate newborns to take their first breath at birth. First, labor contractions temporarily constrict umbilical blood vessels, reducing oxygenated blood flow to the fetus and elevating carbon dioxide levels in the blood. High carbon dioxide levels cause acidosis and stimulate the respiratory center in the brain, triggering the newborn to take a breath.

The first breath typically is taken within 10 seconds of birth, after mucus is aspirated from the infant's mouth and nose. The first breaths inflate the lungs to nearly full capacity and dramatically decrease lung pressure and resistance to blood flow, causing a major circulatory reconfiguration. Pulmonary alveoli open, and alveolar capillaries fill with blood. Amniotic fluid in the lungs drains or is absorbed, and the lungs immediately take over the task of the placenta, exchanging carbon dioxide for oxygen by the process of respiration.

Circulatory Adjustments

The process of clamping and cutting the umbilical cord collapses the umbilical blood vessels. In the absence of medical assistance, this occlusion would occur naturally within 20 minutes of birth because the Wharton's jelly within the umbilical cord would swell in response to the lower temperature outside of the mother's body, and the blood vessels would constrict. Natural occlusion has occurred when the umbilical cord is no longer pulsating. For the most part, the collapsed vessels atrophy and become fibrotic remnants, existing in the mature circulatory system as ligaments of the abdominal wall and liver. The ductus venosus degenerates to become the ligamentum venosum beneath the liver. Only the proximal sections of the two umbilical arteries remain functional, taking on the role of supplying blood to the upper part of the bladder (Figure 28.22).

The breakdown of brown fat occurs automatically upon exposure to cold, so it is an important heat regulator in newborns. During fetal development, the placenta secretes inhibitors that prevent metabolism of brown adipose fat and promote its accumulation in preparation for birth.

Gastrointestinal and Urinary Adjustments

In adults, the gastrointestinal tract harbors bacterial flora—trillions of bacteria that aid in digestion, produce vitamins, and protect from the invasion or replication of pathogens. In stark contrast, the fetal intestine is sterile. The first consumption of breast milk or formula floods the neonatal gastrointestinal tract with beneficial bacteria that begin to establish the bacterial flora.

The fetal kidneys filter blood and produce urine, but the neonatal kidneys are still immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine, making it particularly important for infants to obtain sufficient fluids from breast milk or formula.

HOMEOSTATIC IMBALANCES

Homeostasis in the Newborn: Apgar Score

In the minutes following birth, a newborn must undergo dramatic systemic changes to be able to survive outside the womb. An obstetrician, midwife, or nurse can estimate how well a newborn is doing by obtaining an Apgar score. The Apgar score was introduced in 1952 by the anesthesiologist Dr. Virginia Apgar as a method to assess the effects on the newborn of anesthesia given to the person giving birth. Healthcare providers now use it to assess the general wellbeing of the newborn, whether or not analgesics or anesthetics were used.

Five criteria—skin color, heart rate, reflex, muscle tone, and respiration—are assessed, and each criterion is assigned a score of 0, 1, or 2. Scores are taken at 1 minute after birth and again at 5 minutes after birth. Each time that scores are taken, the five scores are added together. High scores (out of a possible 10) indicate the baby has made the transition from the womb well, whereas lower scores indicate that the baby may be in distress.

The technique for determining an Apgar score is quick and easy, painless for the newborn, and does not require any instruments except for a stethoscope. A convenient way to remember the five scoring criteria is to apply the mnemonic APGAR, for “appearance” (skin color), “pulse” (heart rate), “grimace” (reflex), “activity” (muscle tone), and “respiration.”

Of the five Apgar criteria, heart rate and respiration are the most critical. Poor scores for either of these measurements may indicate the need for immediate medical attention to resuscitate or stabilize the newborn. In general, any score lower than 7 at the 5-minute mark indicates that medical assistance may be needed. A total score below 5 indicates an emergency situation. Normally, a newborn will get an intermediate score of 1 for some of the Apgar criteria and will progress to a 2 by the 5-minute assessment. Scores of 8 or above are normal.

28.6 Lactation

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Describe the structure of the lactating breast
- Summarize the process of lactation
- Explain how the composition of breast milk changes during the first days of lactation and in the course of a single feeding

Lactation is the process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., involution), and induces a substantial metabolic increase in the postpartum person, consuming the fat reserves stored during pregnancy.

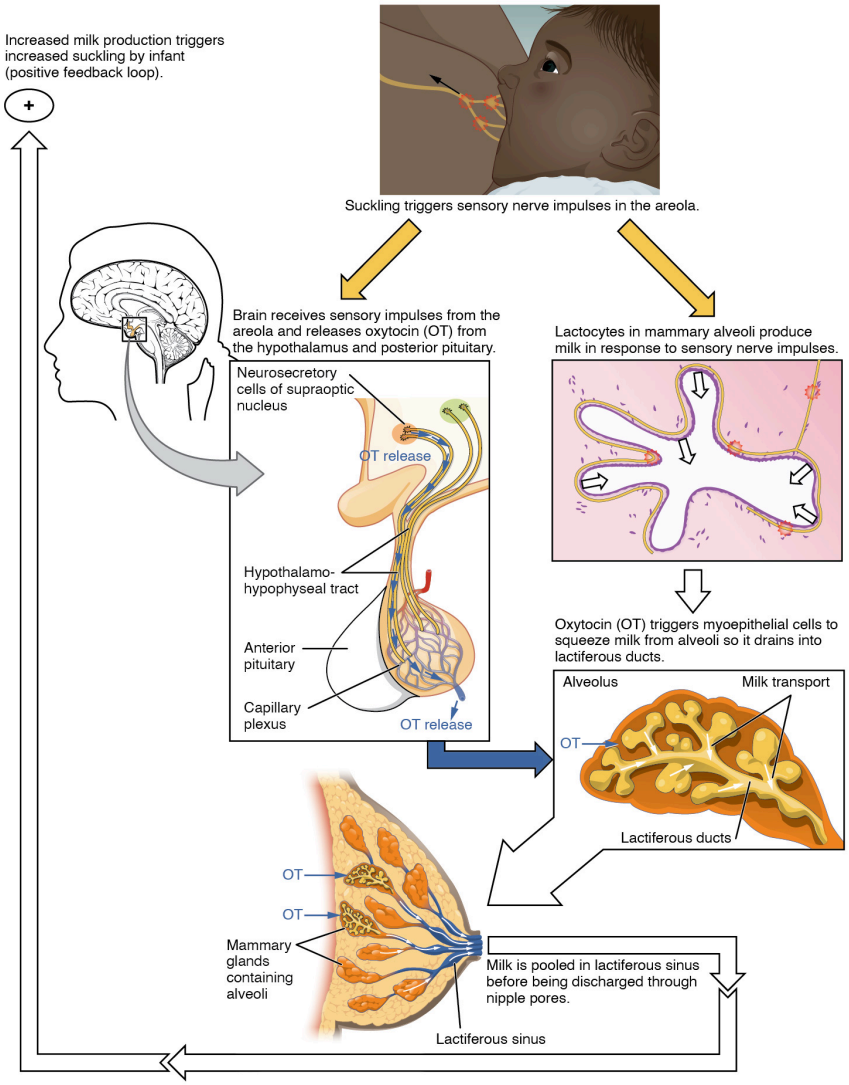


FIGURE 28.23 Let-Down Reflex A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed.

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its pre-pregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.

Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with **colostrum**, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk (Table 28.3). Before childbirth, some people experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

28.7 Patterns of Inheritance

LEARNING OBJECTIVES

By the end of this section, you will be able to:

- Differentiate between genotype and phenotype
- Describe how alleles determine a person's traits
- Summarize Mendel's experiments and relate them to human genetics
- Explain the inheritance of autosomal dominant and recessive and sex-linked genetic disorders

We have discussed the events that lead to the development of a newborn. But what makes each newborn unique? The answer lies, of course, in the DNA in the sperm and oocyte that combined to produce that first diploid cell, the human zygote.

From Genotype to Phenotype

Each human body cell has a full complement of DNA stored in 23 pairs of chromosomes. Figure 28.24 shows the pairs in a systematic arrangement called a **karyotype**. Among these is one pair of chromosomes, called the **sex chromosomes**, that determines the sex of the individual (XX in females, XY in males). The remaining 22 chromosome pairs are called **autosomal chromosomes**. Each of these chromosomes carries hundreds or even thousands of genes, each of which codes for the assembly of a particular protein—that is, genes are "expressed" as proteins. An individual's complete genetic makeup is referred to as their **genotype**. The characteristics that the genes express, whether they are physical, behavioral, or biochemical, are a person's **phenotype**.

In genetics and reproduction, "parent" is often used to describe the individual organisms that contribute genetic material to offspring, usually in the form of gamete cells and their chromosomes. The concept of a genetic parent is distinct from social and legal concepts of parenthood, and may differ from those whom people consider their parents.

You inherit one chromosome in each pair—a full complement of 23—from each parent. This occurs when the sperm and oocyte combine at the moment of your conception. Homologous chromosomes—those that make up a complementary pair—have genes for the same characteristics in the same location on the chromosome. Because one copy of a gene, an **allele**, is inherited from each parent, the alleles in these complementary pairs may vary. Take for example an allele that encodes for dimples. A child may inherit the allele encoding for dimples on the chromosome from the one parent and the allele that encodes for smooth skin (no dimples) on the chromosome from the other parent.

present in a purebred parent. He called dwarfism **recessive** because it was masked in the offspring if one of the purebred parents possessed the dominant characteristic. Note that tallness and dwarfism are variations on the characteristic of height. Mendel called such a variation a **trait**. We now know that these traits are the expression of different alleles of the gene encoding height.

Mendel performed thousands of crosses in pea plants with differing traits for a variety of characteristics. And he repeatedly came up with the same results—among the traits he studied, one was always dominant, and the other was always recessive. (Remember, however, that this dominant–recessive relationship between alleles is not always the case; some alleles are codominant, and sometimes dominance is incomplete.)

Using his understanding of dominant and recessive traits, Mendel tested whether a recessive trait could be lost altogether in a pea lineage or whether it would resurface in a later generation. By crossing the second-generation offspring of purebred parents with each other, he showed that the latter was true: recessive traits reappeared in third-generation plants in a ratio of 3:1 (three offspring having the dominant trait and one having the recessive trait). Mendel then proposed that characteristics such as height were determined by heritable "factors" that were transmitted, one from each parent, and inherited in pairs by offspring.

In the language of genetics, Mendel's theory applied to humans says that if an individual receives two dominant alleles, one from each parent, the individual's phenotype will express the dominant trait. If an individual receives two recessive alleles, then the recessive trait will be expressed in the phenotype. Individuals who have two identical alleles for a given gene, whether dominant or recessive, are said to be homozygous for that gene (homo- = "same"). Conversely, an individual who has one dominant allele and one recessive allele is said to be heterozygous for that gene (hetero- = "different" or "other"). In this case, the dominant trait will be expressed, and the individual will be phenotypically identical to an individual who possesses two dominant alleles for the trait.

It is common practice in genetics to use capital and lowercase letters to represent dominant and recessive alleles. Using Mendel's pea plants as an example, if a tall pea plant is homozygous, it will possess two tall alleles (*TT*). A dwarf pea plant must be homozygous because its dwarfism can only be expressed when two recessive alleles are present (*tt*). A heterozygous pea plant (*Tt*) would be tall and phenotypically indistinguishable from a tall homozygous pea plant because of the dominant tall allele. Mendel deduced that a 3:1 ratio of dominant to recessive would be produced by the random segregation of heritable factors (genes) when crossing two heterozygous pea plants. In other words, for any given gene, parents are equally likely to pass down either one of their alleles to their offspring in a haploid gamete, and the result will be expressed in a dominant–recessive pattern if both parents are heterozygous for the trait.

Because of the random segregation of gametes, the laws of chance and probability come into play when predicting the likelihood of a given phenotype. Consider a cross between an individual with two dominant alleles for a trait (*AA*) and an individual with two recessive alleles for the same trait (*aa*). All of the parental gametes from the dominant individual would be *A*, and all of the parental gametes from the recessive individual would be *a* (Figure 28.25). All of the offspring of that second generation, inheriting one allele from each parent, would have the genotype *Aa*, and the probability of expressing the phenotype of the dominant allele would be 4 out of 4, or 100 percent.

This seems simple enough, but the inheritance pattern gets interesting when the second-generation *Aa* individuals are crossed. In this generation, 50 percent of each parent's gametes are *A* and the other 50 percent are *a*. By Mendel's principle of random segregation, the possible combinations of gametes that the offspring can receive are *AA*, *Aa*, *aA* (which is the same as *Aa*), and *aa*. Because segregation and fertilization are random, each offspring has a 25 percent chance of receiving any of these combinations. Therefore, if an *Aa* × *Aa* cross were performed 1000 times, approximately 250 (25 percent) of the offspring would be *AA*; 500 (50 percent) would be *Aa* (that is, *Aa* plus *aA*); and 250 (25 percent) would be *aa*. The genotypic ratio for this inheritance pattern is 1:2:1. However, we have already established that *AA* and *Aa* (and *aA*) individuals all express the dominant trait (i.e., share the same phenotype), and can therefore be combined into one group. The result is Mendel's third-generation phenotype ratio of 3:1.

genotypes are equally likely to occur: *Nn*, *Nn*, *nn*, and *nn*. That is, every child of this couple would have a 50 percent chance of inheriting neurofibromatosis. This inheritance pattern is shown in Figure 28.26, in a form called a **Punnett square**, named after its creator, the British geneticist Reginald Punnett.

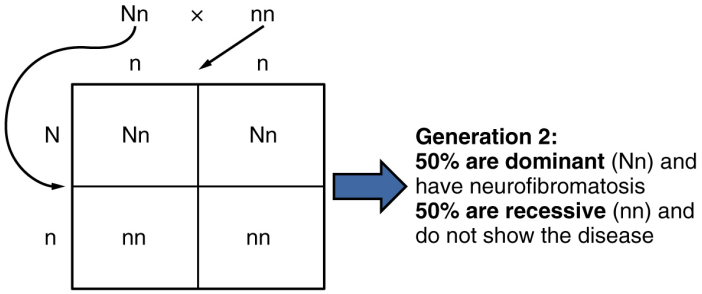


FIGURE 28.26 Autosomal Dominant Inheritance Inheritance pattern of an autosomal dominant disorder, such as neurofibromatosis, is shown in a Punnett square.

Other genetic diseases that are inherited in this pattern are achondroplastic dwarfism, Marfan syndrome, and Huntington's disease. Because autosomal dominant disorders are expressed by the presence of just one gene, an individual with the disorder will know that they have at least one faulty gene. The expression of the disease may manifest later in life, after the childbearing years, which is the case in Huntington's disease (discussed in more detail later in this section).

Autosomal Recessive Inheritance

When a genetic disorder is inherited in an **autosomal recessive** pattern, the disorder corresponds to the recessive phenotype. Heterozygous individuals will not display symptoms of this disorder, because their unaffected gene will compensate. Such an individual is called a **carrier**. Carriers for an autosomal recessive disorder may never know their genotype unless they have a child with the disorder.

An example of an autosomal recessive disorder is cystic fibrosis (CF), which we introduced earlier. CF is characterized by the chronic accumulation of a thick, tenacious mucus in the lungs and digestive tract. Decades ago, children with CF rarely lived to adulthood. With advances in medical technology, the average lifespan in developed countries has increased into middle adulthood. CF is a relatively common disorder that occurs in approximately 30,000 people in the United States. A child born to two CF carriers would have a 25 percent chance of inheriting the disease. This is the same 3:1 dominant:recessive ratio that Mendel observed in his pea plants would apply here. The pattern is shown in Figure 28.27, using a diagram that tracks the likely incidence of an autosomal recessive disorder on the basis of parental genotypes.

On the other hand, a child born to a CF carrier and someone with two unaffected alleles would have a 0 percent probability of inheriting CF, but would have a 50 percent chance of being a carrier. Other examples of autosome recessive genetic illnesses include the blood disorder sickle-cell anemia, the fatal neurological disorder Tay–Sachs disease, and the metabolic disorder phenylketonuria.

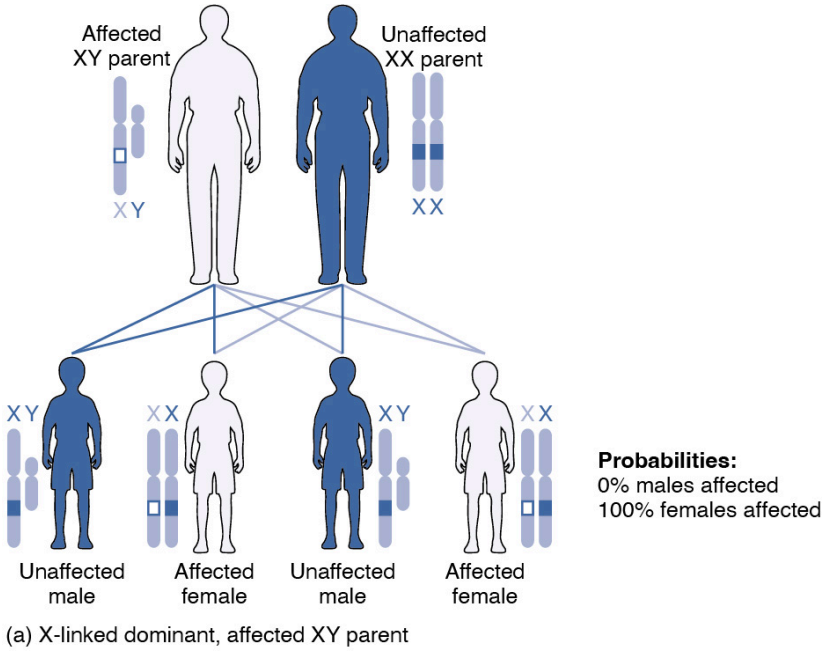


FIGURE 28.28 **X-Linked Patterns of Inheritance** A chart of X-linked dominant inheritance patterns differs depending on which parent is affected with the disease. (credit: U.S. National Library of Medicine)

X-linked recessive inheritance is much more common because females can be carriers of the disease yet still have a normal phenotype. Diseases transmitted by X-linked recessive inheritance include color blindness, the blood-clotting disorder hemophilia, and some forms of muscular dystrophy. For an example of X-linked recessive inheritance, consider parents in which the female is an unaffected carrier and the male is normal. None of the female offspring would have the disease because they receive a normal gene from their male parent. However, they have a 50 percent chance of receiving the disease gene from their female parent and becoming a carrier. In contrast, 50 percent of the male offspring would be affected (Figure 28.29).

With X-linked recessive diseases, males either have the disease or are genotypically normal—they cannot be carriers. Females, however, can be genotypically normal, a carrier who is phenotypically normal, or affected with the disease. A female can inherit the gene for an X-linked recessive illness when the female parent is a carrier or

Expression of Blood Types

Blood type	Genotype	Pattern of inheritance
A	I^AI^A or I^Ai	I^A is dominant to i
B	I^BI^B or I^Bi	I^B is dominant to i
AB	I^AI^B	I^A is co-dominant to I^B
O	ii	Two recessive alleles

TABLE 28.4

Certain combinations of alleles can be lethal, meaning they prevent the individual from developing in utero, or cause a shortened life span. In **recessive lethal** inheritance patterns, a child who is born to two heterozygous (carrier) parents and who inherited the faulty allele from both would not survive. An example of this is Tay–Sachs, a fatal disorder of the nervous system. In this disorder, parents with one copy of the allele for the disorder are carriers. If they both transmit their abnormal allele, their offspring will develop the disease and will die in childhood, usually before age 5.

Dominant lethal inheritance patterns are much more rare because neither heterozygotes nor homozygotes survive. Of course, dominant lethal alleles that arise naturally through mutation and cause miscarriages or stillbirths are never transmitted to subsequent generations. However, some dominant lethal alleles, such as the allele for Huntington's disease, cause a shortened life span but may not be identified until after the person reaches reproductive age and has children. Huntington's disease causes irreversible nerve cell degeneration and death in 100 percent of affected individuals, but it may not be expressed until the individual reaches middle age. In this way, dominant lethal alleles can be maintained in the human population. Individuals with a family history of Huntington's disease are typically offered genetic counseling, which can help them decide whether or not they wish to be tested for the faulty gene.

Mutations

A **mutation** is a change in the sequence of DNA nucleotides that may or may not affect a person's phenotype. Mutations can arise spontaneously from errors during DNA replication, or they can result from environmental insults such as radiation, certain viruses, or exposure to tobacco smoke or other toxic chemicals. Because genes encode for the assembly of proteins, a mutation in the nucleotide sequence of a gene can change amino acid sequence and, consequently, a protein's structure and function. Spontaneous mutations occurring during meiosis are thought to account for many spontaneous abortions (miscarriages).

Chromosomal Disorders

Sometimes a genetic disease is not caused by a mutation in a gene, but by the presence of an incorrect number of chromosomes. For example, Down syndrome is caused by having three copies of chromosome 21. This is known as trisomy 21. The most common cause of trisomy 21 is chromosomal nondisjunction during meiosis. The frequency of nondisjunction events appears to increase with age, so the frequency of bearing a child with Down syndrome increases in females over 36. The age of the male parent matters less because nondisjunction is much less likely to occur in a sperm than in an egg.

Whereas Down syndrome is caused by having three copies of a chromosome, Turner syndrome is caused by having just one copy of the X chromosome. This is known as monosomy. The affected child is always female. Women with Turner syndrome are sterile because their sexual organs do not mature.

Key Terms

acrosomal reaction release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

acrosome cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

afterbirth third stage of childbirth in which the placenta and associated fetal membranes are expelled

allantois finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

allele alternative forms of a gene that occupy a specific locus on a specific gene

amnion transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

amniotic cavity cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

autosomal chromosome in humans, the 22 pairs of chromosomes that are not the sex chromosomes (XX or XY)

autosomal dominant pattern of dominant inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

autosomal recessive pattern of recessive inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

blastocoel fluid-filled cavity of the blastocyst

blastocyst term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

blastomere daughter cell of a cleavage

Braxton Hicks contractions weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

brown adipose tissue highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat

capacitation process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte's outer layers

carrier heterozygous individual who does not display symptoms of a recessive genetic disorder but can transmit the disorder to their offspring

chorion membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi

chorionic membrane precursor to the chorion; forms from extra-embryonic mesoderm cells

chorionic villi projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

cleavage form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

codominance pattern of inheritance that corresponds to the equal, distinct, and simultaneous expression of two different alleles

colostrum thick, yellowish substance secreted from a mother's breasts in the first postpartum days; rich in immunoglobulins

conceptus pre-implantation stage of a fertilized egg and its associated membranes

corona radiata in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

cortical reaction following fertilization, the release of cortical granules from the oocyte's plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

dilation first stage of childbirth, involving an increase in cervical diameter

dominant describes a trait that is expressed both in homozygous and heterozygous form

dominant lethal inheritance pattern in which individuals with one or two copies of a lethal allele do not survive in utero or have a shortened life span

ductus arteriosus shunt in the pulmonary trunk that diverts oxygenated blood back to the aorta

ductus venosus shunt that causes oxygenated blood to bypass the fetal liver on its way to the inferior vena cava

ectoderm primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails

ectopic pregnancy implantation of an embryo outside of the uterus

embryo developing human during weeks 3–8

opening of the cervix as it grows

placentation formation of the placenta; complete by weeks 14–16 of pregnancy

polyspermy penetration of an oocyte by more than one sperm

primitive streak indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

prolactin pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk

Punnett square grid used to display all possible combinations of alleles transmitted by parents to offspring and predict the mathematical probability of offspring inheriting a given genotype

quickening fetal movements that are strong enough to be felt by the mother

recessive describes a trait that is only expressed in homozygous form and is masked in heterozygous form

recessive lethal inheritance pattern in which individuals with two copies of a lethal allele do not survive in utero or have a shortened life span

sex chromosomes pair of chromosomes involved in sex determination; in males, the XY chromosomes; in females, the XX chromosomes

shunt circulatory shortcut that diverts the flow of blood from one region to another

somite one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

syncytiotrophoblast superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

trait variation of an expressed characteristic

trimester division of the duration of a pregnancy into three 3-month terms

trophoblast fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

true labor regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time

umbilical cord connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the mother

vernix caseosa waxy, cheese-like substance that protects the delicate fetal skin until birth

X-linked pattern of inheritance in which an allele is carried on the X chromosome of the 23rd pair

X-linked dominant pattern of dominant inheritance that corresponds to a gene on the X chromosome of the 23rd pair

X-linked recessive pattern of recessive inheritance that corresponds to a gene on the X chromosome of the 23rd pair

yolk sac membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure

zona pellucida thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

zygote fertilized egg; a diploid cell resulting from the fertilization of haploid gametes from the male and female lines

Chapter Review

28.1 Fertilization

Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a thick glycoprotein membrane that lies just outside the oocyte's plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte's zona pellucida. One of the sperm will then break through to the oocyte's plasma membrane and release its haploid nucleus into the oocyte. The oocyte's membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes,

suckling triggers oxytocin release, which stimulates myoepithelial cells to squeeze milk from alveoli. Breast milk then drains toward the nipple pores to be consumed by the infant. Colostrum, the milk produced in the first postpartum days, provides immunoglobulins that increase the newborn's immune defenses. Colostrum, transitional milk, and mature breast milk are ideally suited to each stage of the newborn's development, and breastfeeding helps the newborn's digestive system expel meconium and clear bilirubin. Mature milk changes from the beginning to the end of a feeding. Foremilk quenches the infant's thirst, whereas hindmilk satisfies the infant's appetite.

28.7 Patterns of Inheritance

There are two aspects to a person's genetic makeup. Their genotype refers to the genetic makeup of the chromosomes found in all their cells and the alleles that are passed down from their parents. Their phenotype is the expression of that genotype, based on the interaction of the paired alleles, as well as how environmental conditions affect that expression.

Working with pea plants, Mendel discovered that the factors that account for different traits in parents are discretely transmitted to offspring in pairs, one from each parent. He articulated the principles of random segregation and independent assortment to account for the inheritance patterns he observed. Mendel's factors are genes, with differing variants being referred to as alleles and those alleles being dominant or recessive in expression. Each parent passes one allele for every gene on to offspring, and offspring are equally likely to inherit any combination of allele pairs. When Mendel crossed heterozygous individuals, he repeatedly found a 3:1 dominant–recessive ratio. He correctly postulated that the expression of the recessive trait was masked in heterozygotes but would resurface in their offspring in a predictable manner.

Human genetics focuses on identifying different alleles and understanding how they express themselves. Medical researchers are especially interested in the identification of inheritance patterns for genetic disorders, which provides the means to estimate the risk that a given couple's offspring will inherit a genetic disease or disorder. Patterns of inheritance in humans include autosomal dominance and recessiveness, X-linked dominance and recessiveness, incomplete dominance, codominance, and lethality. A change in the nucleotide sequence of DNA, which may or may not manifest in a phenotype, is called a mutation.

Interactive Link Questions

1. View this time-lapse movie (http://openstax.org/l/conceptus) of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

2. Visit this site (http://openstax.org/l/pregstages) for a summary of the stages of pregnancy, as experienced by the pregnant person, and view the stages of development of the fetus throughout gestation. At what point in fetal development can a regular heartbeat be detected?

Review Questions

3. Sperm and ova are similar in terms of _____.
- a. size
- b. quantity produced per year
- c. chromosome number
- d. flagellar motility

4. Although the male ejaculate contains hundreds of millions of sperm, _____.
- a. most do not reach the oocyte
- b. most are destroyed by the alkaline environment of the uterus
- c. it takes millions to penetrate the outer layers of the oocyte
- d. most are destroyed by capacitation

5. As sperm first reach the oocyte, they will contact the _____.
- a. acrosome
- b. corona radiata
- c. sperm-binding receptors
- d. zona pellucida

6. Fusion of pronuclei occurs during _____.
- a. spermatogenesis
- b. ovulation
- c. fertilization
- d. capacitation

21. Which of these fetal presentations is the easiest for vaginal birth?
   a. complete breech
   b. vertex occiput anterior
   c. frank breech
   d. vertex occiput posterior

22. Which of these shunts exists between the right and left atria?
   a. foramen ovale
   b. ductus venosus
   c. ductus arteriosis
   d. foramen venosus

23. Why is brown fat important?
   a. It is the newborn's primary source of insulation.
   b. It can be broken down to generate heat for thermoregulation.
   c. It can be broken down for energy between feedings.
   d. It can be converted to white fat.

24. Constriction of umbilical blood vessels during vaginal birth _____.
   a. causes respiratory alkalosis
   b. inhibits the respiratory center in the brain
   c. elevates carbon dioxide levels in the blood
   d. both a and b

25. Alveoli are connected to the lactiferous sinuses by _____.
   a. lactocytes
   b. lactiferous ducts
   c. nipple pores
   d. lobules

26. How is colostrum most important to a newborn?
   a. It helps boost the newborn's immune system.
   b. It provides much needed fat.
   c. It satisfies the newborn's thirst.
   d. It satisfies the infant's appetite.

27. Mature breast milk _____.
   a. has more sodium than cow's milk
   b. has more calcium than cow's milk
   c. has more protein than cow's milk
   d. has more fat than cow's milk

28. Marfan syndrome is inherited in an autosomal dominant pattern. Which of the following is true?
   a. Female offspring are more likely to be carriers of the disease.
   b. Male offspring are more likely to inherit the disease.
   c. Male and female offspring have the same likelihood of inheriting the disease.
   d. Female offspring are more likely to inherit the disease.

29. In addition to codominance, the ABO blood group antigens are also an example of _____.
   a. incomplete dominance
   b. X-linked recessive inheritance
   c. multiple alleles
   d. recessive lethal inheritance

30. Zoe has cystic fibrosis. Which of the following is the most likely explanation?
   a. Zoe probably inherited one faulty allele from her father, who is a carrier, and one normal allele from her mother.
   b. Zoe probably inherited one faulty allele from her mother, who must also have cystic fibrosis, and one normal allele from her father.
   c. Zoe must have inherited faulty alleles from both parents, both of whom must also have cystic fibrosis.
   d. Zoe must have inherited faulty alleles from both parents, both of whom are carriers.

Critical Thinking Questions

31. Darcy and Raul are having difficulty conceiving a child. Darcy ovulates every 28 days, and Raul's sperm count is normal. If we could observe Raul's sperm about an hour after ejaculation, however, we'd see that they appear to be moving only sluggishly. When Raul's sperm eventually encounter Darcy's oocyte, they appear to be incapable of generating an adequate acrosomal reaction. Which process has probably gone wrong?

32. On Saturday night, a female has unprotected sex with a male. On Tuesday morning, she experiences the twinge of mid-cycle pain that she typically feels when she is ovulating. This makes her extremely anxious that she might soon learn she is pregnant. Is the concern valid? Why or why not?

33. Approximately 3 weeks after her last menstrual period, a sexually active woman experiences a brief episode of abdominopelvic cramping and minor bleeding. What might be the explanation?

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